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(54) Title: SECRETED EXPRESSED SEQUENCE TAGS (sESTs)

(57) Abstract

Secreted expressed sequence tags (sESTs) isolated from a variety of human tissue sources are provided.

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SECRETED EXPRESSED SEQUENCE TAGS (sESTs)

FIELD OF THE INVENTION

The present invention provides novel polynucleotides which are expressed sequence tags (ESTs) for secreted proteins.

BACKGROUND OF THE INVENTION

Gargantuan efforts have been employed by various investigational projects to randomly sequence portions of naturally-occurring cDNAs. The rationale behind this approach to identification and sequencing genes is founded in two basic principles: (1) that transcribed cDNAs represent the product of the most important genes, namely those that are actually expressed *in vivo*, and (2) that efforts to sequence genes and other portions of the genome of target organisms which are not actually expressed wastes substantial effort on areas not likely to yield genetic information of therapeutic importance. Thus, the high-throughput sequencing efforts focus on only those portions of the genome which are expressed. The randomly produced cDNA sequences represent "expressed sequence tags" or "ESTs", which identify and can be used as probes for the longer, full-length cDNA or genomic sequence from which they were transcribed.

Although this "shortcut" approach to genomic sequencing presents savings of effort compared to sequencing of the complete genome, it still produced a vast array of ESTs which may not be directly useful as protein therapeutics. To date, the majority of protein-related drug discovery has focused on the use of secreted proteins to produce a desired therapeutic effect. Since the EST approach theoretically identifies all expressed proteins, it produces an EST library which contains a mixture of secreted proteins (such as hormones, cytokines and receptors) and non-secreted proteins (such as, for example, metabolic enzymes and cellular structural proteins), without identifying which ESTs correspond to proteins falling into either category. As a result, these methods are not optimally tailored to the needs of investigators searching for secreted proteins because they must separate the secreted "wheat" from the non-secreted "chaff", wasting effort and resources in the process.

Co-assigned U.S. Patent No. 5,536,637, which is incorporated herein by reference, provides methods for focusing genomic sequencing efforts on sequences encoding the secreted proteins which are of most interest for identification of protein therapeutics. The '637 patent discloses a "signal sequence trap" which selectively identifies ESTs for secreted proteins, namely "secreted expressed sequence tags" or "sESTs". It is to these sESTs that the present invention is directed.

SUMMARY OF THE INVENTION

The present invention provides for sESTs isolated from a variety of human RNA/cDNA sources.

In preferred embodiments, the present invention provides an isolated polynucleotide comprising a nucleotide sequence selected from the group consisting of:

SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:8, SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:15, SEQ ID NO:16, SEQ ID NO:17, SEQ ID NO:18, SEQ ID NO:19, SEQ ID NO:20, SEQ ID NO:21, SEQ ID NO:22, SEQ ID NO:23, SEQ ID NO:24, SEQ ID NO:25, SEQ ID NO:26, SEQ ID NO:27, SEQ ID NO:28, SEQ ID NO:29, SEQ ID NO:30, SEQ ID NO:31, SEQ ID NO:32, SEQ ID NO:33, SEQ ID NO:34, SEQ ID NO:35, SEQ ID NO:36, SEQ ID NO:37, SEQ ID NO:38, SEQ ID NO:39, SEQ ID NO:40, SEQ ID NO:41, SEQ ID NO:42, SEQ ID NO:43, SEQ ID NO:44, SEQ ID NO:45, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:49, SEQ ID NO:50, SEQ ID NO:51, SEQ ID NO:52, SEQ ID NO:53, SEQ ID NO:54, SEQ ID NO:55, SEQ ID NO:56, SEQ ID NO:57, SEQ ID NO:58, SEQ ID NO:59, SEQ ID NO:60, SEQ ID NO:61, SEQ ID NO:62, SEQ ID NO:63, SEQ ID NO:64, SEQ ID NO:65, SEQ ID NO:66, SEQ ID NO:67, SEQ ID NO:68, SEQ ID NO:69, SEQ ID NO:70, SEQ ID NO:71, SEQ ID NO:72, SEQ ID NO:73, SEQ ID NO:74, SEQ ID NO:75, SEQ ID NO:76, SEQ ID NO:77, SEQ ID NO:78, SEQ ID NO:79, SEQ ID NO:80, SEQ ID NO:81, SEQ ID NO:82, SEQ ID NO:83, SEQ ID NO:84, SEQ ID NO:85, SEQ ID NO:86, SEQ ID NO:87, SEQ ID NO:88, SEQ ID NO:89, SEQ ID NO:90, SEQ ID NO:91, SEQ ID NO:92, SEQ ID NO:93, SEQ ID NO:94, SEQ ID NO:95, SEQ ID NO:96, SEQ ID NO:97, SEQ ID NO:98, SEQ ID NO:99, SEQ ID NO:100, SEQ ID NO:101, SEQ ID NO:102, SEQ ID NO:103, SEQ ID NO:104, SEQ ID NO:105, SEQ ID NO:106, SEQ ID NO:107, SEQ ID NO:108, SEQ ID NO:109, SEQ ID NO:110, SEQ ID NO:111, SEQ ID NO:112, SEQ ID NO:113, SEQ ID NO:114, SEQ ID NO:115, SEQ ID NO:116, SEQ ID NO:117, SEQ ID NO:118, SEQ ID NO:119, SEQ ID NO:120, SEQ ID NO:121, SEQ ID NO:122, SEQ ID NO:123, SEQ ID NO:124, SEQ ID NO:125, SEQ ID NO:126, SEQ ID NO:127, SEQ ID NO:128, SEQ ID NO:129, SEQ ID NO:130, SEQ ID NO:131, SEQ ID NO:132, SEQ ID NO:133, SEQ ID NO:134, SEQ ID NO:135, SEQ ID NO:136, SEQ ID NO:137, SEQ ID NO:138, SEQ ID NO:139, SEQ ID NO:140, SEQ ID

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or a complement of said sequence.

In other embodiments, the present invention provides an isolated polynucleotide consisting of a nucleotide sequence selected from the group consisting of:

SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:8, SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:15, SEQ ID NO:16, SEQ ID NO:17, SEQ ID NO:18, SEQ ID NO:19, SEQ ID NO:20, SEQ ID NO:21, SEQ ID NO:22, SEQ ID NO:23, SEQ ID NO:24, SEQ ID NO:25, SEQ ID NO:26, SEQ ID NO:27, SEQ ID NO:28, SEQ ID NO:29, SEQ ID NO:30, SEQ ID NO:31, SEQ ID NO:32, SEQ ID NO:33, SEQ ID NO:34, SEQ ID NO:35, SEQ ID NO:36, SEQ ID NO:37, SEQ ID NO:38, SEQ ID NO:39, SEQ ID NO:40, SEQ ID NO:41, SEQ ID NO:42, SEQ ID NO:43, SEQ ID NO:44, SEQ ID NO:45, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:49, SEQ ID NO:50, SEQ ID NO:51, SEQ ID NO:52, SEQ ID NO:53, SEQ ID NO:54, SEQ ID NO:55, SEQ ID NO:56, SEQ ID NO:57, SEQ ID NO:58, SEQ ID NO:59, SEQ ID NO:60, SEQ ID NO:61, SEQ ID NO:62, SEQ ID NO:63, SEQ ID NO:64, SEQ ID NO:65, SEQ ID NO:66, SEQ ID NO:67, SEQ ID NO:68, SEQ ID NO:69, SEQ ID NO:70, SEQ ID NO:71, SEQ ID NO:72, SEQ ID NO:73, SEQ ID NO:74, SEQ ID NO:75, SEQ ID NO:76, SEQ ID NO:77, SEQ ID NO:78, SEQ ID NO:79, SEQ ID NO:80, SEQ ID NO:81, SEQ ID NO:82, SEQ ID NO:83, SEQ ID NO:84, SEQ ID NO:85, SEQ ID NO:86, SEQ ID NO:87, SEQ ID NO:88, SEQ ID NO:89, SEQ ID NO:90, SEQ ID NO:91, SEQ ID NO:92, SEQ ID NO:93, SEQ ID NO:94, SEQ ID NO:95, SEQ ID NO:96, SEQ ID NO:97, SEQ ID NO:98, SEQ ID NO:99, SEQ ID NO:100, SEQ ID NO:101, SEQ ID NO:102, SEQ ID NO:103, SEQ ID NO:104, SEQ ID

NO:105, SEQ ID NO:106, SEQ ID NO:107, SEQ ID NO:108, SEQ ID NO:109, SEQ ID NO:110, SEQ ID NO:111, SEQ ID NO:112, SEQ ID NO:113, SEQ ID NO:114, SEQ ID NO:115, SEQ ID NO:116, SEQ ID NO:117, SEQ ID NO:118, SEQ ID NO:119, SEQ ID NO:120, SEQ ID NO:121, SEQ ID NO:122, SEQ ID NO:123, SEQ ID NO:124, SEQ ID NO:125, SEQ ID NO:126, SEQ ID NO:127, SEQ ID NO:128, SEQ ID NO:129, SEQ ID NO:130, SEQ ID NO:131, SEQ ID NO:132, SEQ ID NO:133, SEQ ID NO:134, SEQ ID NO:135, SEQ ID NO:136, SEQ ID NO:137, SEQ ID NO:138, SEQ ID NO:139, SEQ ID NO:140, SEQ ID NO:141, SEQ ID NO:142, SEQ ID NO:143, SEQ ID NO:144, SEQ ID NO:145, SEQ ID NO:146, SEQ ID NO:147, SEQ ID NO:148, SEQ ID NO:149, SEQ ID NO:150, SEQ ID NO:151, SEQ ID NO:152, SEQ ID NO:153, SEQ ID NO:154, SEQ ID NO:155, SEQ ID NO:156, SEQ ID NO:157, SEQ ID NO:158, SEQ ID NO:159, SEQ ID NO:160, SEQ ID NO:161, SEQ ID NO:162, SEQ ID NO:163, SEQ ID NO:164, SEQ ID NO:165, SEQ ID NO:166, SEQ ID NO:167, SEQ ID NO:168, SEQ ID NO:169, SEQ ID NO:170, SEQ ID NO:171, SEQ ID NO:172, SEQ ID NO:173, SEQ ID NO:174, SEQ ID NO:175, SEQ ID NO:176, SEQ ID NO:177, SEQ ID NO:178, SEQ ID NO:179, SEQ ID NO:180, SEQ ID NO:181, SEQ ID NO:182, SEQ ID NO:183, SEQ ID NO:184, SEQ ID NO:185, SEQ ID NO:186, SEQ ID NO:187, SEQ ID NO:188, SEQ ID NO:189, SEQ ID NO:190, SEQ ID NO:191, SEQ ID NO:192, SEQ ID NO:193, SEQ ID NO:194, SEQ ID NO:195, SEQ ID NO:196, SEQ ID NO:197, SEQ ID NO:198, SEQ ID NO:199, SEQ ID NO:200, SEQ ID NO:201, SEQ ID NO:202, SEQ ID NO:203, SEQ ID NO:204, SEQ ID NO:205, SEQ ID NO:206, SEQ ID NO:207, SEQ ID NO:208, SEQ ID NO:209, SEQ ID NO:210, SEQ ID NO:211, SEQ ID NO:212, SEQ ID NO:213, SEQ ID NO:214, SEQ ID NO:215, SEQ ID NO:216, SEQ ID NO:217, SEQ ID NO:218, SEQ ID NO:219, SEQ ID NO:220, SEQ ID NO:221, SEQ ID NO:222, SEQ ID NO:223, SEQ ID NO:224, SEQ ID NO:225, SEQ ID NO:226, SEQ ID NO:227, SEQ ID NO:228, SEQ ID NO:229, SEQ ID NO:230, SEQ ID NO:231, SEQ ID NO:232, SEQ ID NO:233, SEQ ID NO:234, SEQ ID NO:235, SEQ ID NO:236, SEQ ID NO:237, SEQ ID NO:238, SEQ ID NO:239, SEQ ID NO:240, SEQ ID NO:241, SEQ ID NO:242, SEQ ID NO:243, SEQ ID NO:244, SEQ ID NO:245, SEQ ID NO:246, SEQ ID NO:247, SEQ ID NO:248, SEQ ID NO:249, SEQ ID NO:250, SEQ ID NO:251, SEQ ID NO:252, SEQ ID NO:253, SEQ ID NO:254, SEQ ID NO:255, SEQ ID NO:256, SEQ ID NO:257, SEQ ID

NO:258, SEQ ID NO:259, SEQ ID NO:260, SEQ ID NO:261, SEQ ID NO:262, SEQ ID NO:263, SEQ ID NO:264, SEQ ID NO:265, SEQ ID NO:266, SEQ ID NO:267, SEQ ID NO:268, SEQ ID NO:269, SEQ ID NO:270, SEQ ID NO:271, SEQ ID NO:272, SEQ ID NO:273, SEQ ID NO:274, SEQ ID NO:275, SEQ ID NO:276, SEQ ID NO:277, SEQ ID NO:278, SEQ ID NO:279, SEQ ID NO:280, SEQ ID NO:281, SEQ ID NO:282, SEQ ID NO:283, SEQ ID NO:284, SEQ ID NO:285, SEQ ID NO:286, SEQ ID NO:287, SEQ ID NO:288, SEQ ID NO:289, SEQ ID NO:290, SEQ ID NO:291, SEQ ID NO:292, SEQ ID NO:293, SEQ ID NO:294, SEQ ID NO:295, SEQ ID NO:296, SEQ ID NO:297, SEQ ID NO:298, SEQ ID NO:299, SEQ ID NO:300, SEQ ID NO:301, SEQ ID NO:302, SEQ ID NO:303, SEQ ID NO:304, SEQ ID NO:305, SEQ ID NO:306, SEQ ID NO:307, SEQ ID NO:308, SEQ ID NO:309, SEQ ID NO:310, SEQ ID NO:311, SEQ ID NO:312, SEQ ID NO:313, SEQ ID NO:314, SEQ ID NO:315, SEQ ID NO:316, SEQ ID NO:317, SEQ ID NO:318, SEQ ID NO:319, SEQ ID NO:320, SEQ ID NO:321, SEQ ID NO:322, SEQ ID NO:323, SEQ ID NO:324, SEQ ID NO:325, SEQ ID NO:326, SEQ ID NO:327, SEQ ID NO:328, SEQ ID NO:329, SEQ ID NO:330, SEQ ID NO:331, SEQ ID NO:332, SEQ ID NO:333, SEQ ID NO:334, SEQ ID NO:335, SEQ ID NO:336, SEQ ID NO:337, SEQ ID NO:338, SEQ ID NO:339, SEQ ID NO:340, SEQ ID NO:341, SEQ ID NO:342, SEQ ID NO:343, SEQ ID NO:344, SEQ ID NO:345, SEQ ID NO:346, SEQ ID NO:347, SEQ ID NO:348, SEQ ID NO:349, SEQ ID NO:350, SEQ ID NO:351, SEQ ID NO:352, SEQ ID NO:353, SEQ ID NO:354, SEQ ID NO:355, SEQ ID NO:356, SEQ ID NO:357, SEQ ID NO:358, SEQ ID NO:359, SEQ ID NO:360, SEQ ID NO:361, SEQ ID NO:362, SEQ ID NO:363, SEQ ID NO:364, SEQ ID NO:365, SEQ ID NO:366, SEQ ID NO:367, SEQ ID NO:368, SEQ ID NO:369, SEQ ID NO:370, SEQ ID NO:371, SEQ ID NO:372, SEQ ID NO:373, SEQ ID NO:374, SEQ ID NO:375, SEQ ID NO:376, SEQ ID NO:377, SEQ ID NO:378, SEQ ID NO:379, SEQ ID NO:380, SEQ ID NO:381, SEQ ID NO:382, SEQ ID NO:383, SEQ ID NO:384, SEQ ID NO:385, SEQ ID NO:386, SEQ ID NO:387, SEQ ID NO:388, SEQ ID NO:389, SEQ ID NO:390, SEQ ID NO:391, SEQ ID NO:392, SEQ ID NO:393, SEQ ID NO:394, SEQ ID NO:395, SEQ ID NO:396, SEQ ID NO:397, SEQ ID NO:398, SEQ ID NO:399, SEQ ID NO:400, SEQ ID NO:401, SEQ ID NO:402, SEQ ID NO:403, SEQ ID NO:404, SEQ ID NO:405, SEQ ID NO:406, SEQ ID NO:407, SEQ ID NO:408, SEQ ID NO:409, SEQ ID NO:410, SEQ ID

NO:411, SEQ ID NO:412, SEQ ID NO:413, SEQ ID NO:414, SEQ ID NO:415, SEQ ID NO:416, SEQ ID NO:417, SEQ ID NO:418, SEQ ID NO:419, SEQ ID NO:420, SEQ ID NO:421, SEQ ID NO:422, SEQ ID NO:423, SEQ ID NO:424, SEQ ID NO:425, SEQ ID NO:426, SEQ ID NO:427, SEQ ID NO:428, SEQ ID NO:429, SEQ ID NO:430, SEQ ID NO:431, SEQ ID NO:432, SEQ ID NO:433, SEQ ID NO:434, SEQ ID NO:435, SEQ ID NO:436, SEQ ID NO:437, SEQ ID NO:438, SEQ ID NO:439, SEQ ID NO:440, SEQ ID NO:441, SEQ ID NO:442, SEQ ID NO:443, SEQ ID NO:444, SEQ ID NO:445, SEQ ID NO:446, SEQ ID NO:447, SEQ ID NO:448, SEQ ID NO:449, SEQ ID NO:450, SEQ ID NO:451, SEQ ID NO:452, SEQ ID NO:453, SEQ ID NO:454, SEQ ID NO:455, SEQ ID NO:456, SEQ ID NO:457, SEQ ID NO:458, SEQ ID NO:459, SEQ ID NO:460, SEQ ID NO:461, SEQ ID NO:462, SEQ ID NO:463, SEQ ID NO:464, SEQ ID NO:465, SEQ ID NO:466, SEQ ID NO:467, SEQ ID NO:468, SEQ ID NO:469, SEQ ID NO:470, SEQ ID NO:471, SEQ ID NO:472, SEQ ID NO:473, SEQ ID NO:474, SEQ ID NO:475, SEQ ID NO:476, SEQ ID NO:477, SEQ ID NO:478, SEQ ID NO:479, SEQ ID NO:480, SEQ ID NO:481, SEQ ID NO:482, SEQ ID NO:483, SEQ ID NO:484, SEQ ID NO:485, SEQ ID NO:486, SEQ ID NO:487, SEQ ID NO:488, SEQ ID NO:489, SEQ ID NO:490, SEQ ID NO:491, SEQ ID NO:492, SEQ ID NO:493, SEQ ID NO:494, SEQ ID NO:495, SEQ ID NO:496, SEQ ID NO:497, SEQ ID NO:498, SEQ ID NO:499, SEQ ID NO:500, SEQ ID NO:501, SEQ ID NO:502, SEQ ID NO:503, SEQ ID NO:504, SEQ ID NO:505, SEQ ID NO:506, SEQ ID NO:507, SEQ ID NO:508, SEQ ID NO:509, SEQ ID NO:510, SEQ ID NO:511, SEQ ID NO:512, SEQ ID NO:513, SEQ ID NO:514, SEQ ID NO:515, SEQ ID NO:516, SEQ ID NO:517, SEQ ID NO:518, SEQ ID NO:519, SEQ ID NO:520, SEQ ID NO:521, SEQ ID NO:522, SEQ ID NO:523, SEQ ID NO:524, SEQ ID NO:525, SEQ ID NO:526, SEQ ID NO:527, SEQ ID NO:528, SEQ ID NO:529, SEQ ID NO:530, SEQ ID NO:531, SEQ ID NO:532, SEQ ID NO:533, SEQ ID NO:534, SEQ ID NO:535, SEQ ID NO:536, SEQ ID NO:537, SEQ ID NO:538, SEQ ID NO:539, SEQ ID NO:540, SEQ ID NO:541, SEQ ID NO:542, SEQ ID NO:543, SEQ ID NO:544, SEQ ID NO:545, SEQ ID NO:546, SEQ ID NO:547, SEQ ID NO:548, SEQ ID NO:549, SEQ ID NO:550, SEQ ID NO:551, SEQ ID NO:552, SEQ ID NO:553, SEQ ID NO:554, SEQ ID NO:555, SEQ ID NO:556, SEQ ID NO:557, SEQ ID NO:558, SEQ ID NO:559, SEQ ID NO:560, SEQ ID NO:561, SEQ ID NO:562, SEQ ID NO:563, SEQ ID

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NO:1157, SEQ ID NO:1158, SEQ ID NO:1159, SEQ ID NO:1160, SEQ ID NO:1161, SEQ ID NO:1162, SEQ ID NO:1163, SEQ ID NO:1164, SEQ ID NO:1165, SEQ ID NO:1166, SEQ ID NO:1167, SEQ ID NO:1168, SEQ ID NO:1169, SEQ ID NO:1170, SEQ ID NO:1171, SEQ ID NO:1172, SEQ ID NO:1173, SEQ ID NO:1174, SEQ ID NO:1175, SEQ ID NO:1176, SEQ ID NO:1177, SEQ ID NO:1178, SEQ ID NO:1179, SEQ ID NO:1180, SEQ ID NO:1181, SEQ ID NO:1182, SEQ ID NO:1183, SEQ ID NO:1184, SEQ ID NO:1185, SEQ ID NO:1186, SEQ ID NO:1187, SEQ ID NO:1188, SEQ ID NO:1189, SEQ ID NO:1190, SEQ ID NO:1191, SEQ ID NO:1192, SEQ ID NO:1193, SEQ ID NO:1194, SEQ ID NO:1195, SEQ ID NO:1196, SEQ ID NO:1197, SEQ ID NO:1198, SEQ ID NO:1199, SEQ ID NO:1200, SEQ ID NO:1201, SEQ ID NO:1202, SEQ ID NO:1203, SEQ ID NO:1204, SEQ ID NO:1205, SEQ ID NO:1206, SEQ ID NO:1207, SEQ ID NO:1208, SEQ ID NO:1209, SEQ ID NO:1210, SEQ ID NO:1211, SEQ ID NO:1212, SEQ ID NO:1213, SEQ ID NO:1214, SEQ ID NO:1215, SEQ ID NO:1216, SEQ ID NO:1217, SEQ ID NO:1218, SEQ ID NO:1219, SEQ ID NO:1220, SEQ ID NO:1221, SEQ ID NO:1222, SEQ ID NO:1223, SEQ ID NO:1224, SEQ ID NO:1225, SEQ ID NO:1226, SEQ ID NO:1227, SEQ ID NO:1228, SEQ ID NO:1229, SEQ ID NO:1230, SEQ ID NO:1231, SEQ ID NO:1232, SEQ ID NO:1233, SEQ ID NO:1234, SEQ ID NO:1235, SEQ ID NO:1236, SEQ ID NO:1237, SEQ ID NO:1238, SEQ ID NO:1239, SEQ ID NO:1240, SEQ ID NO:1241, SEQ ID NO:1242, SEQ ID NO:1243, SEQ ID NO:1244, SEQ ID NO:1245, SEQ ID NO:1246, SEQ ID NO:1247, SEQ ID NO:1248, SEQ ID NO:1249, SEQ ID NO:1250, SEQ ID NO:1251, SEQ ID NO:1252, SEQ ID NO:1253, SEQ ID NO:1254, SEQ ID NO:1255, SEQ ID NO:1256, SEQ ID NO:1257, SEQ ID NO:1258, SEQ ID NO:1259, SEQ ID NO:1260, SEQ ID NO:1261, SEQ ID NO:1262, SEQ ID NO:1263, SEQ ID NO:1264, SEQ ID NO:1265, SEQ ID NO:1266, SEQ ID NO:1267, SEQ ID NO:1268, SEQ ID NO:1269, SEQ ID NO:1270, SEQ ID NO:1271, SEQ ID NO:1272, SEQ ID NO:1273, SEQ ID NO:1274, SEQ ID NO:1275, SEQ ID NO:1276, SEQ ID NO:1277, SEQ ID NO:1278, SEQ ID NO:1279, SEQ ID NO:1280, SEQ ID NO:1281, SEQ ID NO:1282, SEQ ID NO:1283, SEQ ID NO:1284, SEQ ID NO:1285, SEQ ID NO:1286, SEQ ID NO:1287, SEQ ID NO:1288, SEQ ID NO:1289, SEQ ID NO:1290, SEQ ID NO:1291, SEQ ID NO:1292, SEQ ID

NO:1293, SEQ ID NO:1294, SEQ ID NO:1295, SEQ ID NO:1296, SEQ ID NO:1297, SEQ ID NO:1298, SEQ ID NO:1299, SEQ ID NO:1300, SEQ ID NO:1301, SEQ ID NO:1302, SEQ ID NO:1303, SEQ ID NO:1304, SEQ ID NO:1305, SEQ ID NO:1306, SEQ ID NO:1307, SEQ ID NO:1308, SEQ ID NO:1309, SEQ ID NO:1310, SEQ ID NO:1311, SEQ ID NO:1312, SEQ ID NO:1313, SEQ ID NO:1314, SEQ ID NO:1315, SEQ ID NO:1316, SEQ ID NO:1317, SEQ ID NO:1318, SEQ ID NO:1319, SEQ ID NO:1320, SEQ ID NO:1321, SEQ ID NO:1322, SEQ ID NO:1323, SEQ ID NO:1324, SEQ ID NO:1325, SEQ ID NO:1326, SEQ ID NO:1327, SEQ ID NO:1328, SEQ ID NO:1329, SEQ ID NO:1330, SEQ ID NO:1331, SEQ ID NO:1332, SEQ ID NO:1333, SEQ ID NO:1334, SEQ ID NO:1335, SEQ ID NO:1336, SEQ ID NO:1337, SEQ ID NO:1338, SEQ ID NO:1339, SEQ ID NO:1340, SEQ ID NO:1341, SEQ ID NO:1342, SEQ ID NO:1343, SEQ ID NO:1344, SEQ ID NO:1345, SEQ ID NO:1346, SEQ ID NO:1347, SEQ ID NO:1348, SEQ ID NO:1349, SEQ ID NO:1350, SEQ ID NO:1351, SEQ ID NO:1352, SEQ ID NO:1353, SEQ ID NO:1354, SEQ ID NO:1355, SEQ ID NO:1356, SEQ ID NO:1357, SEQ ID NO:1358, SEQ ID NO:1359, SEQ ID NO:1360, SEQ ID NO:1361, SEQ ID NO:1362, SEQ ID NO:1363, SEQ ID NO:1364, SEQ ID NO:1365, SEQ ID NO:1366, SEQ ID NO:1367, SEQ ID NO:1368, SEQ ID NO:1369, SEQ ID NO:1370, SEQ ID NO:1371, SEQ ID NO:1372, SEQ ID NO:1373, SEQ ID NO:1374, SEQ ID NO:1375, SEQ ID NO:1376, SEQ ID NO:1377, SEQ ID NO:1378, SEQ ID NO:1379, SEQ ID NO:1380, SEQ ID NO:1381, SEQ ID NO:1382, SEQ ID NO:1383, SEQ ID NO:1384, SEQ ID NO:1385, SEQ ID NO:1386, SEQ ID NO:1387, SEQ ID NO:1388, SEQ ID NO:1389, SEQ ID NO:1390, SEQ ID NO:1391, SEQ ID NO:1392, SEQ ID NO:1393, SEQ ID NO:1394, SEQ ID NO:1395, SEQ ID NO:1396, SEQ ID NO:1397, SEQ ID NO:1398, SEQ ID NO:1399, SEQ ID NO:1400, SEQ ID NO:1401, SEQ ID NO:1402, SEQ ID NO:1403, SEQ ID NO:1404, SEQ ID NO:1405, SEQ ID NO:1406, SEQ ID NO:1407, SEQ ID NO:1408, SEQ ID NO:1409, SEQ ID NO:1410, SEQ ID NO:1411, SEQ ID NO:1412, SEQ ID NO:1413, SEQ ID NO:1414, SEQ ID NO:1415, SEQ ID NO:1416, SEQ ID NO:1417, SEQ ID NO:1418, SEQ ID NO:1419, SEQ ID NO:1420, SEQ ID NO:1421, SEQ ID NO:1422, SEQ ID NO:1423, SEQ ID NO:1424, SEQ ID NO:1425, SEQ ID NO:1426, SEQ ID NO:1427, SEQ ID NO:1428, SEQ ID

NO:1429, SEQ ID NO:1430, SEQ ID NO:1431, SEQ ID NO:1432, SEQ ID NO:1433, SEQ ID NO:1434, SEQ ID NO:1435, SEQ ID NO:1436, SEQ ID NO:1437, SEQ ID NO:1438, SEQ ID NO:1439, SEQ ID NO:1440, SEQ ID NO:1441, SEQ ID NO:1442, SEQ ID NO:1443, SEQ ID NO:1444, SEQ ID NO:1445, SEQ ID NO:1446, SEQ ID NO:1447, SEQ ID NO:1448, SEQ ID NO:1449, SEQ ID NO:1450, SEQ ID NO:1451, SEQ ID NO:1452, SEQ ID NO:1453, SEQ ID NO:1454, SEQ ID NO:1455, SEQ ID NO:1456, SEQ ID NO:1457, SEQ ID NO:1458, SEQ ID NO:1459, SEQ ID NO:1460, SEQ ID NO:1461, SEQ ID NO:1462, SEQ ID NO:1463, SEQ ID NO:1464, SEQ ID NO:1465, SEQ ID NO:1466, SEQ ID NO:1467, SEQ ID NO:1468, SEQ ID NO:1469, SEQ ID NO:1470, SEQ ID NO:1471, SEQ ID NO:1472, SEQ ID NO:1473, SEQ ID NO:1474, SEQ ID NO:1475, SEQ ID NO:1476, SEQ ID NO:1477, SEQ ID NO:1478, SEQ ID NO:1479, SEQ ID NO:1480, SEQ ID NO:1481, SEQ ID NO:1482, SEQ ID NO:1483, SEQ ID NO:1484, SEQ ID NO:1485, SEQ ID NO:1486, SEQ ID NO:1487, SEQ ID NO:1488, SEQ ID NO:1489, SEQ ID NO:1490, SEQ ID NO:1491, SEQ ID NO:1492, SEQ ID NO:1493, SEQ ID NO:1494, SEQ ID NO:1495, SEQ ID NO:1496, SEQ ID NO:1497, SEQ ID NO:1498, SEQ ID NO:1499, and SEQ ID NO:1500;

or a complement of said sequence.

In further embodiments, the present invention provides an isolated polynucleotide consisting essentially of a nucleotide sequence selected from the group consisting of:

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NO:1125, SEQ ID NO:1126, SEQ ID NO:1127, SEQ ID NO:1128, SEQ ID NO:1129, SEQ ID NO:1130, SEQ ID NO:1131, SEQ ID NO:1132, SEQ ID NO:1133, SEQ ID NO:1134, SEQ ID NO:1135, SEQ ID NO:1136, SEQ ID NO:1137, SEQ ID NO:1138, SEQ ID NO:1139, SEQ ID NO:1140, SEQ ID NO:1141, SEQ ID NO:1142, SEQ ID NO:1143, SEQ ID NO:1144, SEQ ID NO:1145, SEQ ID NO:1146, SEQ ID NO:1147, SEQ ID NO:1148, SEQ ID NO:1149, SEQ ID NO:1150, SEQ ID NO:1151, SEQ ID NO:1152, SEQ ID NO:1153, SEQ ID NO:1154, SEQ ID NO:1155, SEQ ID NO:1156, SEQ ID NO:1157, SEQ ID NO:1158, SEQ ID NO:1159, SEQ ID NO:1160, SEQ ID NO:1161, SEQ ID NO:1162, SEQ ID NO:1163, SEQ ID NO:1164, SEQ ID NO:1165, SEQ ID NO:1166, SEQ ID NO:1167, SEQ ID NO:1168, SEQ ID NO:1169, SEQ ID NO:1170, SEQ ID NO:1171, SEQ ID NO:1172, SEQ ID NO:1173, SEQ ID NO:1174, SEQ ID NO:1175, SEQ ID NO:1176, SEQ ID NO:1177, SEQ ID NO:1178, SEQ ID NO:1179, SEQ ID NO:1180, SEQ ID NO:1181, SEQ ID NO:1182, SEQ ID NO:1183, SEQ ID NO:1184, SEQ ID NO:1185, SEQ ID NO:1186, SEQ ID NO:1187, SEQ ID NO:1188, SEQ ID NO:1189, SEQ ID NO:1190, SEQ ID NO:1191, SEQ ID NO:1192, SEQ ID NO:1193, SEQ ID NO:1194, SEQ ID NO:1195, SEQ ID NO:1196, SEQ ID NO:1197, SEQ ID NO:1198, SEQ ID NO:1199, SEQ ID NO:1200, SEQ ID NO:1201, SEQ ID NO:1202, SEQ ID NO:1203, SEQ ID NO:1204, SEQ ID NO:1205, SEQ ID NO:1206, SEQ ID NO:1207, SEQ ID NO:1208, SEQ ID NO:1209, SEQ ID NO:1210, SEQ ID NO:1211, SEQ ID NO:1212, SEQ ID NO:1213, SEQ ID NO:1214, SEQ ID NO:1215, SEQ ID NO:1216, SEQ ID NO:1217, SEQ ID NO:1218, SEQ ID NO:1219, SEQ ID NO:1220, SEQ ID NO:1221, SEQ ID NO:1222, SEQ ID NO:1223, SEQ ID NO:1224, SEQ ID NO:1225, SEQ ID NO:1226, SEQ ID NO:1227, SEQ ID NO:1228, SEQ ID NO:1229, SEQ ID NO:1230, SEQ ID NO:1231, SEQ ID NO:1232, SEQ ID NO:1233, SEQ ID NO:1234, SEQ ID NO:1235, SEQ ID NO:1236, SEQ ID NO:1237, SEQ ID NO:1238, SEQ ID NO:1239, SEQ ID NO:1240, SEQ ID NO:1241, SEQ ID NO:1242, SEQ ID NO:1243, SEQ ID NO:1244, SEQ ID NO:1245, SEQ ID NO:1246, SEQ ID NO:1247, SEQ ID NO:1248, SEQ ID NO:1249, SEQ ID NO:1250, SEQ ID NO:1251, SEQ ID NO:1252, SEQ ID NO:1253, SEQ ID NO:1254, SEQ ID NO:1255, SEQ ID NO:1256, SEQ ID NO:1257, SEQ ID NO:1258, SEQ ID NO:1259, SEQ ID NO:1260, SEQ ID

NO:1261, SEQ ID NO:1262, SEQ ID NO:1263, SEQ ID NO:1264, SEQ ID NO:1265, SEQ ID NO:1266, SEQ ID NO:1267, SEQ ID NO:1268, SEQ ID NO:1269, SEQ ID NO:1270, SEQ ID NO:1271, SEQ ID NO:1272, SEQ ID NO:1273, SEQ ID NO:1274, SEQ ID NO:1275, SEQ ID NO:1276, SEQ ID NO:1277, SEQ ID NO:1278, SEQ ID NO:1279, SEQ ID NO:1280, SEQ ID NO:1281, SEQ ID NO:1282, SEQ ID NO:1283, SEQ ID NO:1284, SEQ ID NO:1285, SEQ ID NO:1286, SEQ ID NO:1287, SEQ ID NO:1288, SEQ ID NO:1289, SEQ ID NO:1290, SEQ ID NO:1291, SEQ ID NO:1292, SEQ ID NO:1293, SEQ ID NO:1294, SEQ ID NO:1295, SEQ ID NO:1296, SEQ ID NO:1297, SEQ ID NO:1298, SEQ ID NO:1299, SEQ ID NO:1300, SEQ ID NO:1301, SEQ ID NO:1302, SEQ ID NO:1303, SEQ ID NO:1304, SEQ ID NO:1305, SEQ ID NO:1306, SEQ ID NO:1307, SEQ ID NO:1308, SEQ ID NO:1309, SEQ ID NO:1310, SEQ ID NO:1311, SEQ ID NO:1312, SEQ ID NO:1313, SEQ ID NO:1314, SEQ ID NO:1315, SEQ ID NO:1316, SEQ ID NO:1317, SEQ ID NO:1318, SEQ ID NO:1319, SEQ ID NO:1320, SEQ ID NO:1321, SEQ ID NO:1322, SEQ ID NO:1323, SEQ ID NO:1324, SEQ ID NO:1325, SEQ ID NO:1326, SEQ ID NO:1327, SEQ ID NO:1328, SEQ ID NO:1329, SEQ ID NO:1330, SEQ ID NO:1331, SEQ ID NO:1332, SEQ ID NO:1333, SEQ ID NO:1334, SEQ ID NO:1335, SEQ ID NO:1336, SEQ ID NO:1337, SEQ ID NO:1338, SEQ ID NO:1339, SEQ ID NO:1340, SEQ ID NO:1341, SEQ ID NO:1342, SEQ ID NO:1343, SEQ ID NO:1344, SEQ ID NO:1345, SEQ ID NO:1346, SEQ ID NO:1347, SEQ ID NO:1348, SEQ ID NO:1349, SEQ ID NO:1350, SEQ ID NO:1351, SEQ ID NO:1352, SEQ ID NO:1353, SEQ ID NO:1354, SEQ ID NO:1355, SEQ ID NO:1356, SEQ ID NO:1357, SEQ ID NO:1358, SEQ ID NO:1359, SEQ ID NO:1360, SEQ ID NO:1361, SEQ ID NO:1362, SEQ ID NO:1363, SEQ ID NO:1364, SEQ ID NO:1365, SEQ ID NO:1366, SEQ ID NO:1367, SEQ ID NO:1368, SEQ ID NO:1369, SEQ ID NO:1370, SEQ ID NO:1371, SEQ ID NO:1372, SEQ ID NO:1373, SEQ ID NO:1374, SEQ ID NO:1375, SEQ ID NO:1376, SEQ ID NO:1377, SEQ ID NO:1378, SEQ ID NO:1379, SEQ ID NO:1380, SEQ ID NO:1381, SEQ ID NO:1382, SEQ ID NO:1383, SEQ ID NO:1384, SEQ ID NO:1385, SEQ ID NO:1386, SEQ ID NO:1387, SEQ ID NO:1388, SEQ ID NO:1389, SEQ ID NO:1390, SEQ ID NO:1391, SEQ ID NO:1392, SEQ ID NO:1393, SEQ ID NO:1394, SEQ ID NO:1395, SEQ ID NO:1396, SEQ ID

NO:1397, SEQ ID NO:1398, SEQ ID NO:1399, SEQ ID NO:1400, SEQ ID NO:1401, SEQ ID NO:1402, SEQ ID NO:1403, SEQ ID NO:1404, SEQ ID NO:1405, SEQ ID NO:1406, SEQ ID NO:1407, SEQ ID NO:1408, SEQ ID NO:1409, SEQ ID NO:1410, SEQ ID NO:1411, SEQ ID NO:1412, SEQ ID NO:1413, SEQ ID NO:1414, SEQ ID NO:1415, SEQ ID NO:1416, SEQ ID NO:1417, SEQ ID NO:1418, SEQ ID NO:1419, SEQ ID NO:1420, SEQ ID NO:1421, SEQ ID NO:1422, SEQ ID NO:1423, SEQ ID NO:1424, SEQ ID NO:1425, SEQ ID NO:1426, SEQ ID NO:1427, SEQ ID NO:1428, SEQ ID NO:1429, SEQ ID NO:1430, SEQ ID NO:1431, SEQ ID NO:1432, SEQ ID NO:1433, SEQ ID NO:1434, SEQ ID NO:1435, SEQ ID NO:1436, SEQ ID NO:1437, SEQ ID NO:1438, SEQ ID NO:1439, SEQ ID NO:1440, SEQ ID NO:1441, SEQ ID NO:1442, SEQ ID NO:1443, SEQ ID NO:1444, SEQ ID NO:1445, SEQ ID NO:1446, SEQ ID NO:1447, SEQ ID NO:1448, SEQ ID NO:1449, SEQ ID NO:1450, SEQ ID NO:1451, SEQ ID NO:1452, SEQ ID NO:1453, SEQ ID NO:1454, SEQ ID NO:1455, SEQ ID NO:1456, SEQ ID NO:1457, SEQ ID NO:1458, SEQ ID NO:1459, SEQ ID NO:1460, SEQ ID NO:1461, SEQ ID NO:1462, SEQ ID NO:1463, SEQ ID NO:1464, SEQ ID NO:1465, SEQ ID NO:1466, SEQ ID NO:1467, SEQ ID NO:1468, SEQ ID NO:1469, SEQ ID NO:1470, SEQ ID NO:1471, SEQ ID NO:1472, SEQ ID NO:1473, SEQ ID NO:1474, SEQ ID NO:1475, SEQ ID NO:1476, SEQ ID NO:1477, SEQ ID NO:1478, SEQ ID NO:1479, SEQ ID NO:1480, SEQ ID NO:1481, SEQ ID NO:1482, SEQ ID NO:1483, SEQ ID NO:1484, SEQ ID NO:1485, SEQ ID NO:1486, SEQ ID NO:1487, SEQ ID NO:1488, SEQ ID NO:1489, SEQ ID NO:1490, SEQ ID NO:1491, SEQ ID NO:1492, SEQ ID NO:1493, SEQ ID NO:1494, SEQ ID NO:1495, SEQ ID NO:1496, SEQ ID NO:1497, SEQ ID NO:1498, SEQ ID NO:1499, and SEQ ID NO:1500;

or a complement of said sequence.

In yet other embodiments, the present invention provides an isolated polynucleotide comprising a nucleotide sequence which hybridizes to a sequence selected from the group consisting of:

SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:8, SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:15, SEQ ID NO:16, SEQ ID NO:17, SEQ ID NO:18, SEQ ID NO:19, SEQ ID NO:20, SEQ

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NO:1493, SEQ ID NO:1494, SEQ ID NO:1495, SEQ ID NO:1496, SEQ ID NO:1497, SEQ ID NO:1498, SEQ ID NO:1499, and SEQ ID NO:1500;

or to a complement of said sequence.

The invention also provides for proteins encoded by the above-described polynucleotides.

DETAILED DESCRIPTION

The nucleotide sequences of the sESTs of the present invention are reported in the Sequence Listing below. Table 2 lists the "Clone ID Nos." assigned by applicants to each SEQ ID NO: in the Sequence Listing.

Table 2

Each pair of entries in this table consists of the SEQ ID NO (e.g., 1, 2, etc.) followed by the Clone ID No. for such sequence (e.g., B11, B18, etc.).

	1	B11	21	C3	41	C639	61	D148
	2	B18	22	C32	42	C641	62	D154
	3	B21	23	C141	43	C642	63	D167
	4	B26	24	C143	44	C645	64	D179
	5	B40	25	C180	45	D4	65	D188
	6	B115	26	C195	46	D7	66	D196
	7	B121	27	C293	47	D14	67	D200
	8	B124	28	C312	48	D15	68	D203
	9	B125	29	C539	49	D27	69	D233
	10	B142	30	C544	50	D68	70	D252
	11	B196	31	C547	51	D69	71	D286
	12	B208	32	C571	52	D81	72	D303
	13	B224	33	C604	53	D100	73	D304
	14	B227	34	C607	54	D101	74	D305
	15	B232	35	C608	55	D104	75	D310
	16	B236	36	C610	56	D105	76	D311
	17	B238	37	C617	57	D115	77	D318
	18	B255	38	C626	58	D121	78	D327
	19	C1	39	C627	59	D133	79	D329
	20	C2	40	C636	60	D143	80	E1

	81	E4	115	H291	149	J139	183	M141
	82	E5	116	H306	150	J143	184	M152
	83	E11	117	H383	151	J156	185	M194
	84	E12	118	H426	152	J168	186	M230
5	85	E14	119	H438	153	J297	187	M273
	86	E18	120	H541	154	J317	188	M292
	87	G1	121	H545	155	J322	189	M301
	88	G12	122	H657	156	J422	190	M313
	89	G16	123	H698	157	J435	191	M328
10	90	G20	124	H758	158	J509	192	M338
	91	G21	125	H770	159	J512	193	O7
	92	G26	126	H849	160	J532	194	O47
	93	G31	127	H920	161	J546	195	O67
	94	G40	128	H978	162	J598	196	O75
15	95	G46	129	H999	163	J635	197	O99
	96	G53	130	H1004	164	J638	198	O135
	97	G55	131	H1010	165	J708	199	O139
	98	G58	132	H1045	166	J731	200	O268
	99	G68	133	H1052	167	M4	201	O276
20	100	G85	134	H1075	168	M6	202	O289
	101	G86	135	H1096	169	M43	203	O338
	102	G99	136	H1116	170	M60	204	O349
	103	G103	137	H1165	171	M68	205	O351
	104	G107	138	H1301	172	M71	206	O372
25	105	G108	139	H1408	173	M88	207	O386
	106	G112	140	H1413	174	M97	208	O417
	107	G114	141	H1456	175	M100	209	O418
	108	H45	142	I5	176	M114	210	O463
	109	H162	143	I28	177	M120	211	S10
30	110	H165	144	I32	178	M121	212	S34
	111	H171	145	J5	179	M125	213	S70
	112	H174	146	J54	180	M126	214	S169
	113	H225	147	J66	181	M128	215	S185
	114	H236	148	J135	182	M137	216	S195

	217	AA20	251	AJ6	285	AM72	319	AP137
	218	AA35	252	AJ8	286	AM93	320	AP76
	219	AB10	253	AJ52	287	AK679	321	AP87
	220	AA240	254	AJ53	288	AK684	322	AP90
5	221	AA244	255	AJ54	289	AK699	323	AP150
	222	AA246	256	AJ78	290	AM155	324	AP159
	223	AA287	257	AJ80	291	AM167	325	AP160
	224	AA299	258	AK368	292	AM207	326	AP162
	225	AA318	259	AJ127	293	AM217	327	AP168
10	226	AB45	260	AJ142	294	AM224	328	AP179
	227	AA36	261	AJ143	295	AM226	329	AP197
	228	AA363	262	AC339	296	AM235	330	AP215
	229	AA365	263	AC370	297	AM259	331	AP224
	230	AA351	264	AL14	298	AM266	332	AP226
15	231	AB290	265	AK401	299	AM267	333	AP242
	232	AC41	266	AK438	300	AM277	334	AP250
	233	AC18	267	AK583	301	AM279	335	AQ11
	234	AC175	268	AK585	302	AC387	336	AQ2
	235	AC114	269	AK598	303	AC395	337	AQ21
20	236	AC111	270	AK604	304	AC410	338	AQ23
	237	AC100	271	AK609	305	AC412	339	AQ3
	238	AC222	272	AK620	306	AC423	340	AQ34
	239	AC325	273	AM10	307	AJ146	341	AQ5
	240	AI44	274	AM104	308	AJ147	342	AR15
25	241	AI6	275	AM123	309	AJ156	343	AR22
	242	AI86	276	AM137	310	AJ168	344	AR28
	243	AJ1	277	AM15	311	AJ169	345	AR3
	244	AJ10	278	AM16	312	AJ172	346	AR34
	245	AJ13	279	AM30	313	AJ173	347	AR42
30	246	AJ15	280	AM38	314	AJ174	348	AR54
	247	AJ20	281	AM39	315	AK528	349	AR61
	248	AJ21	282	AM42	316	AP116	350	AM282
	249	AJ26	283	AM46	317	AP120	351	AM307
	250	AJ27	284	AM66	318	AP135	352	AM349

	353	AM372	387	AR310	421	AM616	455	AM921
	354	AM392	388	AR323	422	AM622	456	AM931
	355	AM400	389	AR324	423	AM625	457	AM973
	356	AM430	390	AR325	424	AM666	458	AM996
5	357	AP11	391	AR349	425	AM686	459	AS56
	358	AP2	392	AR360	426	AM704	460	AS61
	359	AP56	393	AR364	427	AM726	461	AS63
	360	AP57	394	AR400	428	AM728	462	AS65
	361	AP58	395	AR415	429	AM735	463	AS83
10	362	AP60	396	AR417	430	AM741	464	AS85
	363	AP67	397	AM558	431	AM742	465	AS86
	364	AP7	398	AM566	432	AM754	466	AS88
	365	AQ53	399	AM600	433	AM781	467	AT107
	366	AQ54	400	AR420	434	AM795	468	AT111
15	367	AQ61	401	AR437	435	AM814	469	AT138
	368	AQ64	402	AR440	436	AM833	470	AT140
	369	AQ71	403	AR446	437	AM838	471	AT142
	370	AQ73	404	AR450	438	AT16	472	AT146
	371	AQ83	405	AR452	439	AT19	473	AT151
20	372	AM1075	406	AR455	440	AT20	474	AT157
	373	AM1076	407	AR463	441	AT4	475	AT181
	374	AM1083	408	AR464	442	AT53	476	AT97
	375	AR100	409	AR467	443	AT63	477	AS239
	376	AR69	410	AR474	444	AT64	478	AT226
25	377	AM1017	411	AR475	445	AT74	479	AT259
	378	AM1032	412	AS15	446	AT94	480	AT260
	379	AM1036	413	AS20	447	AT95	481	AT265
	380	AM1045	414	AS23	448	AM1000	482	AT280
	381	AM1060	415	AS31	449	AM856	483	AT340
30	382	AM1067	416	AS47	450	AM885	484	AT351
	383	AR253	417	AS48	451	AM889	485	AT352
	384	AK642	418	AS7	452	AM892	486	AT356
	385	AK647	419	AM610	453	AM910	487	AT359
	386	AK650	420	AM614	454	AM918	488	AT361

	489	AS252	523	AU161	557	AW106	591	BE28
	490	AS263	524	AU164	558	AW107	592	BE3
	491	AS264	525	AZ285	559	AW109	593	BE34
	492	AS268	526	AZ286	560	AW133	594	BE9
5	493	AS271	527	AZ287	561	AW140	595	AZ12
	494	AS294	528	AZ290	562	AW92	596	AZ22
	495	AS301	529	AZ188	563	AW95	597	AZ32
	496	AS330	530	AZ191	564	AW98	598	AZ45
	497	AS144	531	AZ204	565	BA185	599	AZ46
10	498	AS152	532	AZ219	566	BA204	600	BF143
	499	AS157	533	AW170	567	BA210	601	BF146
	500	AS162	534	AW176	568	BA226	602	BF157
	501	AS164	535	AW178	569	BG1	603	BF160
	502	AS167	536	AW179	570	BG13	604	BF169
15	503	AS180	537	AW182	571	BG3	605	BF171
	504	AS186	538	AW185	572	BG33	606	BF176
	505	AS187	539	AW189	573	BG36	607	BF178
	506	AU36	540	AW192	574	BG37	608	AS196
	507	AU39	541	AW194	575	BG40	609	AS202
20	508	AU43	542	AW199	576	BG43	610	AS209
	509	AU47	543	AW222	577	BG48	611	AS216
	510	AU50	544	AW231	578	BG58	612	AS230
	511	AU59	545	AZ261	579	BG72	613	AS232
	512	AU71	546	AZ264	580	BG73	614	AX101
25	513	AU101	547	AZ302	581	BF101	615	AX104
	514	AU102	548	AZ303	582	BF132	616	AX107
	515	AU105	549	AK649	583	AZ69	617	AX109
	516	AU106	550	AK663	584	BD51	618	AX122
	517	AU107	551	AR336	585	BD53	619	AX124
30	518	AU115	552	AR356	586	BD65	620	AX127
	519	AU118	553	AR398	587	BD66	621	AX128
	520	AU122	554	AR399	588	BD73	622	AX130
	521	AU138	555	AM1016	589	BD77	623	AX132
	522	AU139	556	AW105	590	BD80	624	AX136

	625	AX137	659	BG274	693	AW33	727	BG504
	626	AX143	660	BG276	694	AW36	728	BG510
	627	AX146	661	AX12	695	AW47	729	BG511
	628	AX51	662	AX17	696	AW49	730	BG513
5	629	AX55	663	AX256	697	AW52	731	BG516
	630	AX56	664	AX30	698	AW60	732	BG518
	631	AX60	665	AX32	699	AW66	733	BG526
	632	AX65	666	AX34	700	AW76	734	BG528
	633	AX78	667	AX49	701	AY241	735	BG552
10	634	AX80	668	AX6	702	AY259	736	BG553
	635	AX81	669	AX8	703	AY268	737	BG556
	636	AX92	670	AZ180	704	BA123	738	AX309
	637	AX97	671	BG191	705	BA134	739	AX315
	638	AX98	672	BG193	706	BA170	740	AX318
15	639	AX99	673	BG199	707	BA176	741	AY186
	640	AZ109	674	BG201	708	BA178	742	AY190
	641	AZ114	675	BG219	709	BA179	743	AY200
	642	BF286	676	BG220	710	BA216	744	AY208
	643	BF290	677	BG221	711	BA233	745	AY211
20	644	BF314	678	BG225	712	BD372	746	AY283
	645	BG236	679	BG228	713	BD375	747	AY289
	646	BG237	680	BG442	714	BD379	748	AY304
	647	BG240	681	BG449	715	BD380	749	AY307
	648	BG241	682	BG457	716	BD403	750	AY318
25	649	BG248	683	BG458	717	BD407	751	AY333
	650	BG249	684	BG461	718	BD409	752	AY334
	651	BG250	685	BG465	719	BD413	753	AY342
	652	BG251	686	BG467	720	BD414	754	AY358
	653	BG255	687	BG471	721	BG481	755	AY362
30	654	BG260	688	BG59	722	BG482	756	BF190
	655	BG267	689	AW12	723	BG492	757	BF191
	656	BG271	690	AW22	724	BG494	758	BF193
	657	BG272	691	AW24	725	BG495	759	BF197
	658	BG273	692	AW32	726	BG503	760	BF208

	761	BF211	795	BG373	829	BD174	863	BI17
	762	BF216	796	BG374	830	BD176	864	BI2
	763	BF221	797	BG379	831	BD177	865	BI24
	764	BF227	798	BG386	832	BD178	866	BI25
5	765	BF228	799	BG388	833	BD183	867	BI3
	766	BF245	800	BG389	834	BE50	868	BI36
	767	BF250	801	BG391	835	BE64	869	BI37
	768	BF258	802	BG393	836	BE89	870	BI39
	769	BF259	803	BG396	837	BG490	871	BI40
10	770	BF263	804	BG409	838	BG491	872	BI41
	771	BF270	805	BG411	839	BG501	873	BI46
	772	BF273	806	BG414	840	BG502	874	BM1
	773	BG280	807	BG420	841	BG512	875	BM17
	774	BG283	808	HW105	842	BG532	876	BM4
15	775	BG284	809	BB54	843	BK162	877	BM41
	776	BG288	810	BD101	844	BK165	878	BM46
	777	BG296	811	BD104	845	BK167	879	BM69
	778	BG305	812	BD107	846	BK171	880	BM88
	779	BG306	813	BD109	847	BK179	881	BM90
20	780	BG309	814	BD119	848	BK180	882	BA106
	781	BG324	815	BD121	849	BK183	883	BA12
	782	BG327	816	BD127	850	BK186	884	BA32
	783	BG329	817	BD128	851	BK194	885	BA38
	784	BG332	818	BD132	852	BK200	886	BA40
25	785	BG334	819	BD136	853	BK206	887	BA71
	786	BG335	820	BD137	854	BK216	888	BA79
	787	BG350	821	BD140	855	BK231	889	BA8
	788	BG356	822	BD144	856	BK232	890	BA88
	789	BG357	823	BD151	857	BK236	891	BA90
30	790	BG363	824	BD154	858	BK237	892	BA91
	791	BG365	825	BD164	859	BK241	893	BA98
	792	BG366	826	BD165	860	BK243	894	BK15
	793	BG368	827	BD169	861	BK246	895	BK17
	794	BG372	828	BD170	862	BK253	896	BK24

	897	BK257	931	AY428	965	BK146	999	BG139
	898	BK26	932	AY437	966	BK155	1000	BG140
	899	BK260	933	AY440	967	BK158	1001	BG141
	900	BK265	934	AY442	968	BK75	1002	BG142
5	901	BK270	935	AY449	969	BK78	1003	BG145
	902	BK271	936	AY457	970	BK92	1004	BG148
	903	BK280	937	AY470	971	BK93	1005	BG151
	904	BK284	938	AY487	972	BK95	1006	BG156
	905	BK286	939	AY489	973	BK96	1007	BG158
10	906	BK29	940	AY511	974	BM101	1008	BG160
	907	BK291	941	BE153	975	BM117	1009	BG168
	908	BK295	942	BF327	976	BM124	1010	BG170
	909	BK296	943	BI64	977	BM139	1011	BG171
	910	BK299	944	BI66	978	BM154	1012	BG172
15	911	BK304	945	BI75	979	BM155	1013	BG173
	912	BK307	946	BI80	980	BM158	1014	BG93
	913	BK308	947	BI81	981	BM94	1015	BG95
	914	BK339	948	BI82	982	AY102	1016	BI102
	915	BK34	949	BI86	983	AY107	1017	BI103
20	916	BK343	950	BI87	984	AY122	1018	BI107
	917	BK40	951	BI88	985	AY131	1019	BI110
	918	BK41	952	BI91	986	AY137	1020	BI114
	919	BK48	953	BI92	987	AY140	1021	BI117
	920	BK49	954	BK102	988	AY147	1022	BI120
25	921	BK57	955	BK105	989	AY157	1023	BI122
	922	BK59	956	BK107	990	AY160	1024	BI124
	923	BK61	957	BK112	991	AY183	1025	BI126
	924	BK68	958	BK114	992	AY93	1026	BI127
	925	BL341	959	BK115	993	BG102	1027	BI129
30	926	AY398	960	BK117	994	BG104	1028	BI133
	927	AY406	961	BK120	995	BG112	1029	BI139
	928	AY407	962	BK130	996	BG125	1030	BI150
	929	AY408	963	BK134	997	BG132	1031	BI164
	930	AY421	964	BK142	998	BG137	1032	BI97

1033	BI98	1067	BQ58	1101	BO71	1135	BL209
1034	BI99	1068	BD189	1102	BO87	1136	BL210
1035	BS1	1069	BD194	1103	BO9	1137	BL211
1036	BS54	1070	BD199	1104	BD235	1138	BL219
1037	BS58	1071	BD200	1105	BD240	1139	BL220
1038	BS81	1072	BD201	1106	BD241	1140	BL229
1039	BS89	1073	BD208	1107	BD244	1141	BL230
1040	BH100	1074	BD209	1108	BD247	1142	BL243
1041	BH106	1075	BD213	1109	BD251	1143	BL247
1042	BH111	1076	BD214	1110	BD257	1144	BL249
1043	BH123	1077	BD222	1111	BD260	1145	BL255
1044	BH131	1078	BH19	1112	BD262	1146	BL257
1045	BH157	1079	BH195	1113	BD265	1147	BL271
1046	BH297	1080	BH2	1114	BD268	1148	BL274
1047	BH306	1081	BH227	1115	BD522	1149	BL30
1048	BH309	1082	BH272	1116	BD538	1150	BL67
1049	BH316	1083	BH276	1117	BD544	1151	BL73
1050	BH323	1084	BH281	1118	BD548	1152	BL89
1051	BH339	1085	BH41	1119	BD561	1153	BD420
1052	BH365	1086	BH51	1120	BL147	1154	BD423
1053	BH389	1087	BH66	1121	BL15	1155	BD426
1054	BH392	1088	BH7	1122	BL152	1156	BD427
1055	BJ54	1089	BH87	1123	BL156	1157	BD428
1056	BJ62	1090	BH90	1124	BL160	1158	BD438
1057	BJ66	1091	BJ20	1125	BL178	1159	BD441
1058	BJ67	1092	BJ27	1126	BL179	1160	BD445
1059	BJ69	1093	BJ29	1127	BL183	1161	BD473
1060	BJ70	1094	BJ38	1128	BL185	1162	BD486
1061	BJ75	1095	BJ39	1129	BL186	1163	BD489
1062	BJ76	1096	BJ9	1130	BL187	1164	BD492
1063	BJ78	1097	BO11	1131	BL194	1165	BD512
1064	BJ87	1098	BO20	1132	BL196	1166	BL106
1065	BQ20	1099	BO4	1133	BL201	1167	BL310
1066	BQ3	1100	BO52	1134	BL205	1168	BN1

	1169	BN107	1203	BD351	1237	BN351	1271	BP22
	1170	BN12	1204	BN189	1238	BN354	1272	BP24
	1171	BN130	1205	BN201	1239	BN365	1273	BP25
	1172	BN132	1206	BN212	1240	BN422	1274	BT99
5	1173	BN133	1207	BN280	1241	BN425	1275	BP28
	1174	BN139	1208	BN284	1242	BN439	1276	BP3
	1175	BN141	1209	BN329	1243	BN460	1277	BP4
	1176	BN153	1210	BN331	1244	BN461	1278	BP43
	1177	BN156	1211	BN591	1245	BN463	1279	BP47
10	1178	BN171	1212	BO153	1246	BN472	1280	BP504
	1179	BN174	1213	BO157	1247	BN473	1281	BP506
	1180	BN180	1214	BO159	1248	BO100	1282	BP508
	1181	BN246	1215	BO166	1249	BO107	1283	BP521
	1182	BN267	1216	BO178	1250	BO114	1284	BP528
15	1183	BN268	1217	BO189	1251	BO121	1285	BP530
	1184	BN33	1218	BO194	1252	BO126	1286	BP532
	1185	BN40	1219	BO210	1253	BO133	1287	BP537
	1186	BN48	1220	BO212	1254	BO137	1288	BP544
	1187	BN5	1221	BO213	1255	BO398	1289	BP545
20	1188	BN563	1222	BO218	1256	BO399	1290	BP55
	1189	BN65	1223	BO226	1257	BO401	1291	BP567
	1190	BN69	1224	BO279	1258	BO432	1292	BP569
	1191	BN81	1225	BO301	1259	BO528	1293	BP57
	1192	BN97	1226	BO323	1260	BO535	1294	BP590
25	1193	BN99	1227	BO358	1261	BO538	1295	BP61
	1194	BD286	1228	BO365	1262	BO549	1296	BP70
	1195	BD288	1229	BO385	1263	BO551	1297	BP71
	1196	BD297	1230	BO250	1264	BO93	1298	BP780
	1197	BD316	1231	BO254	1265	BP101	1299	BP783
30	1198	BD317	1232	BO256	1266	BP118	1300	BP784
	1199	BD321	1233	BO260	1267	BP121	1301	BP791
	1200	BD327	1234	BO261	1268	BP15	1302	BP797
	1201	BD335	1235	BO273	1269	BP19	1303	BP806
	1202	BD339	1236	BN342	1270	BP21	1304	BP809

1305	BP810	1339	BV243	1373	CC71	1407	BR572
1306	BP813	1340	BV248	1374	CC76	1408	BR559
1307	BP814	1341	BV250	1375	CC78	1409	BR538
1308	BP815	1342	BV259	1376	CC81	1410	BR537
1309	BP820	1343	BV273	1377	CC89	1411	BR533
1310	BP84	1344	BV275	1378	CD124	1412	BR500
1311	BP919	1345	BV49	1379	CD128	1413	BR48
1312	BP925	1346	BV51	1380	CD140	1414	BR475
1313	BQ115	1347	BV66	1381	CD145	1415	BR436
1314	BQ129	1348	BV70	1382	CD146	1416	BR434
1315	BS116	1349	BV71	1383	CD173	1417	BR4
1316	BT101	1350	BV72	1384	CD194	1418	BR346
1317	BT133	1351	BV73	1385	CD31	1419	BR342
1318	BT139	1352	BV88	1386	CD50	1420	BR338
1319	BT33	1353	BW345	1387	CF50	1421	BR333
1320	BT4	1354	CB25	1388	CF62	1422	BR332
1321	BW13	1355	CB3	1389	CF78	1423	BR212
1322	BW18	1356	CB30	1390	CF85	1424	BR195
1323	BW2	1357	CB37	1391	CF89	1425	BR194
1324	BW51	1358	CC144	1392	BR814	1426	BR19
1325	BW61	1359	CC145	1393	BR782	1427	BR141
1326	BW83	1360	CC149	1394	BR778	1428	BR122
1327	BV185	1361	CC153	1395	BR77	1429	BR107
1328	BV195	1362	CC162	1396	BR767	1430	BR1010
1329	BV200	1363	CC25	1397	BR758	1431	BR101
1330	BV202	1364	CC31	1398	BR733	1432	BR1008
1331	BV204	1365	CC322	1399	BR719	1433	BQ135
1332	BV206	1366	CC39	1400	BR711	1434	BP913
1333	BV210	1367	CC397	1401	BR71	1435	BP911
1334	BV212	1368	CC403	1402	BR63	1436	BP897
1335	BV227	1369	CC46	1403	BR616	1437	BP895
1336	BV238	1370	CC50	1404	BR610	1438	BP894
1337	BV239	1371	CC59	1405	BR607	1439	BP893
1338	BV241	1372	CC69	1406	BR595	1440	BP884

	1441	BP883	1475	BU65
	1442	BP875	1476	BU68
	1443	BP870	1477	BU76
	1444	BP859	1478	BV106
5	1445	BP837	1479	BV112
	1446	BP833	1480	BV123
	1447	BP499	1481	BV124
	1448	BP492	1482	BV126
	1449	BP488	1483	BV128
10	1450	BP484	1484	BV131
	1451	BP483	1485	BV133
	1452	BP481	1486	BV134
	1453	BP475	1487	BV135
	1454	BN418	1488	BV138
15	1455	BN415	1489	BV139
	1456	BN405	1490	BV140
	1457	BN394	1491	BV141
	1458	BN390	1492	BV145
	1459	BN387	1493	BV15
20	1460	BN379	1494	BV158
	1461	BN377	1495	BV160
	1462	BR84	1496	BV172
	1463	BR853	1497	BV180
	1464	BR854	1498	BV21
25	1465	BR884	1499	BV27
	1466	BT160	1500	BV29
	1467	BU165		
	1468	BU29		
	1469	BU44		
30	1470	BU45		
	1471	BU53		
	1472	BU57		
	1473	BU6		
	1474	BU60		

The "Clone ID No." for a particular clone consists of one or two letters followed by a number. The letters designate the tissue source from which the sEST was isolated. Table 3 below lists the various sources which were run through applicants' signal sequence trap. Thus, the tissue source for a particular sEST sequence can be identified in Table 3 by the one and two letter designations used in the relevant "Clone ID No.". For example, a clone designated as "BA312" would have been isolated from a human placenta (26 yrs.) library (i.e., selectin "BA") as indicated in Table 3.

As used herein, "polynucleotide" includes single- and double-stranded RNAs, DNAs and RNA:DNA hybrids.

As used herein a "secreted" protein is one which, when expressed in a suitable host cell, is transported across or through a membrane, including transport as a result of signal sequences in its amino acid sequence. "Secreted" proteins include without limitation proteins secreted wholly (e.g., soluble proteins) or partially (e.g. , receptors) from the cell in which they are expressed. "Secreted" proteins also include without limitation proteins which are transported across the membrane of the endoplpasmic reticulum.

Fragments of the proteins of the present invention which are capable of exhibiting biological activity are also encompassed by the present invention. Fragments of the protein may be in linear form or they may be cyclized using known methods, for example, as described in H.U. Saragovi, *et al.*, Bio/Technology 10, 773-778 (1992) and in R.S. McDowell, *et al.*, J. Amer. Chem. Soc. 114, 9245-9253 (1992), both of which are incorporated herein by reference. Such fragments may be fused to carrier molecules such as immunoglobulins for many purposes, including increasing the valency of protein binding sites. For example, fragments of the protein may be fused through "linker" sequences to the Fc portion of an immunoglobulin. For a bivalent form of the protein, such a fusion could be to the Fc portion of an IgG molecule. Other immunoglobulin isotypes may also be used to generate such fusions. For example, a protein - IgM fusion would generate a decavalent form of the protein of the invention.

The present invention also provides both full-length and mature forms of the disclosed proteins. The full-length form of the such proteins is identified in the sequence listing by translation of the nucleotide sequence of each disclosed clone. The mature form of such protein may be obtained by expression of the disclosed full-length polynucleotide (preferably those deposited with ATCC) in a suitable mammalian cell or other host cell. The sequence of the mature form of the protein may also be determinable from the amino acid sequence of the full-length form.

The present invention also provides genes corresponding to the cDNA sequences disclosed herein. The corresponding genes can be isolated in accordance with known methods using the sequence information disclosed herein. Such methods include the preparation of probes or primers from the disclosed sequence information for identification and/or amplification of genes in appropriate genomic libraries or other sources of genomic materials.

Where the protein of the present invention is membrane-bound (e.g., is a receptor), the present invention also provides for soluble forms of such protein. In such forms part or all of the intracellular and transmembrane domains of the protein are deleted such that the protein is fully secreted from the cell in which it is expressed. The intracellular and transmembrane domains of proteins of the invention can be identified in accordance with known techniques for determination of such domains from sequence information.

Species homologs of the disclosed polynucleotides and proteins are also provided by the present invention. Species homologs may be isolated and identified by making suitable probes or primers from the sequences provided herein and screening a suitable nucleic acid source from the desired species.

The invention also encompasses allelic variants of the disclosed polynucleotides or proteins; that is, naturally-occurring alternative forms of the isolated polynucleotide which also encode proteins which are identical, homologous or related to that encoded by the polynucleotides disclosed herein.

The invention also includes polynucleotides with sequences complementary to those of the polynucleotides disclosed herein.

The present invention also includes polynucleotides capable of hybridizing, preferably under reduced stringency conditions, more preferably under stringent conditions, most preferably under highly stringent conditions, to polynucleotides described herein. Examples of stringency conditions are shown in Table 1 below: highly stringent conditions are those that are at least as stringent as, for example, conditions A-F; stringent conditions are at least as stringent as, for example, conditions G-L; and reduced stringency conditions are at least as stringent as, for example, conditions M-R.

Table 1

Stringency Condition	Polynucleotide Hybrid	Hybrid Length (bp)‡	Hybridization Temperature and Buffer†	Wash Temperature and Buffer†
A	DNA:DNA	≥ 50	65°C; 1xSSC -or- 42°C; 1xSSC, 50% formamide	65°C; 0.3xSSC
B	DNA:DNA	<50	T_B*; 1xSSC	T_B*; 1xSSC
C	DNA:RNA	≥ 50	67°C; 1xSSC -or- 45°C; 1xSSC, 50% formamide	67°C; 0.3xSSC
D	DNA:RNA	<50	T_D*; 1xSSC	T_D*; 1xSSC
E	RNA:RNA	≥ 50	70°C; 1xSSC -or- 50°C; 1xSSC, 50% formamide	70°C; 0.3xSSC
F	RNA:RNA	<50	T_F*; 1xSSC	T_F*; 1xSSC
G	DNA:DNA	≥ 50	65°C; 4xSSC -or- 42°C; 4xSSC, 50% formamide	65°C; 1xSSC
H	DNA:DNA	<50	T_H*; 4xSSC	T_H*; 4xSSC
I	DNA:RNA	≥ 50	67°C; 4xSSC -or- 45°C; 4xSSC, 50% formamide	67°C; 1xSSC
J	DNA:RNA	<50	T_J*; 4xSSC	T_J*; 4xSSC
K	RNA:RNA	≥ 50	70°C; 4xSSC -or- 50°C; 4xSSC, 50% formamide	67°C; 1xSSC
L	RNA:RNA	<50	T_L*; 2xSSC	T_L*; 2xSSC
M	DNA:DNA	≥ 50	50°C; 4xSSC -or- 40°C; 6xSSC, 50% formamide	50°C; 2xSSC
N	DNA:DNA	<50	T_N*; 6xSSC	T_N*; 6xSSC
O	DNA:RNA	≥ 50	55°C; 4xSSC -or- 42°C; 6xSSC, 50% formamide	55°C; 2xSSC
P	DNA:RNA	<50	T_P*; 6xSSC	T_P*; 6xSSC
Q	RNA:RNA	≥ 50	60°C; 4xSSC -or- 45°C; 6xSSC, 50% formamide	60°C; 2xSSC
R	RNA:RNA	<50	T_R*; 4xSSC	T_R*; 4xSSC

[‡]: The hybrid length is that anticipated for the hybridized region(s) of the hybridizing polynucleotides. When hybridizing a polynucleotide to a target polynucleotide of unknown sequence, the hybrid length is assumed to be that of the hybridizing polynucleotide. When polynucleotides of known sequence are hybridized, the hybrid length can be determined by aligning the sequences of the polynucleotides and identifying the region or regions of optimal sequence complementarity.

[†]: SSPE (1xSSPE is 0.15M NaCl, 10mM NaH_2PO_4, and 1.25mM EDTA, pH 7.4) can be substituted for SSC (1xSSC is 0.15M NaCl and 15mM sodium citrate) in the hybridization and wash buffers; washes are performed for 15 minutes after hybridization is complete.

*T_B - T_R: The hybridization temperature for hybrids anticipated to be less than 50 base pairs in length should be 5-10°C less than the melting temperature (T_m) of the hybrid, where T_m is determined according to the following equations. For hybrids less than 18 base pairs in length, T_m(°C) = 2(# of A + T bases) + 4(# of G + C bases). For hybrids between 18 and 49 base pairs in length, T_m(°C) = 81.5 + 16.6($\log$ [Na^+]) + 0.41(%G+C) - (600/N), where N is the number of bases in the hybrid, and [Na^+] is the concentration of sodium ions in the hybridization buffer ([Na^+] for 1xSSC = 0.165 M).

Additional examples of stringency conditions for polynucleotide hybridization are provided in Sambrook, J., E.F. Fritsch, and T. Maniatis, 1989, *Molecular Cloning: A Laboratory Manual*, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY, chapters 9 and 11, and *Current Protocols in Molecular Biology*, 1995, F.M. Ausubel et al., eds., John Wiley & Sons, Inc., sections 2.10 and 6.3-6.4, incorporated herein by reference.

Preferably, such hybridizing polynucleotides have at least 70% sequence identity (more preferably, at least 80% identity; most preferably at least 90% or 95% identity) with the polynucleotide of the present invention to which they hybridize, where sequence identity is determined by comparing the sequences of the hybridizing polynucleotides when aligned so as to maximize overlap and identity while minimizing sequence gaps. The isolated polynucleotide encoding the protein of the invention may be operably linked to an expression control sequence such as the pMT2 or pED expression vectors disclosed in Kaufman *et al.*, Nucleic Acids Res. 19, 4485-4490 (1991), in order to produce the protein recombinantly. Many suitable expression control sequences are known in the art. General methods of expressing recombinant proteins are also known and are exemplified in R. Kaufman, Methods in Enzymology 185, 537-566 (1990). As defined herein "operably linked" means that the isolated polynucleotide of the invention and an expression control

sequence are situated within a vector or cell in such a way that the protein is expressed by a host cell which has been transformed (transfected) with the ligated polynucleotide/expression control sequence.

A number of types of cells may act as suitable host cells for expression of the protein. Mammalian host cells include, for example, monkey COS cells, Chinese Hamster Ovary (CHO) cells, human kidney 293 cells, human epidermal A431 cells, human Colo205 cells, 3T3 cells, CV-1 cells, other transformed primate cell lines, normal diploid cells, cell strains derived from in vitro culture of primary tissue, primary explants, HeLa cells, mouse L cells, BHK, HL-60, U937, HaK or Jurkat cells.

Alternatively, it may be possible to produce the protein in lower eukaryotes such as yeast or in prokaryotes such as bacteria. Potentially suitable yeast strains include *Saccharomyces cerevisiae, Schizosaccharomyces pombe, Kluyveromyces* strains, *Candida,* or any yeast strain capable of expressing heterologous proteins. Potentially suitable bacterial strains include *Escherichia coli, Bacillus subtilis, Salmonella typhimurium,* or any bacterial strain capable of expressing heterologous proteins. If the protein is made in yeast or bacteria, it may be necessary to modify the protein produced therein, for example by phosphorylation or glycosylation of the appropriate sites, in order to obtain the functional protein. Such covalent attachments may be accomplished using known chemical or enzymatic methods.

The protein may also be produced by operably linking the isolated polynucleotide of the invention to suitable control sequences in one or more insect expression vectors, and employing an insect expression system. Materials and methods for baculovirus/insect cell expression systems are commercially available in kit form from, *e.g.*, Invitrogen, San Diego, California, U.S.A. (the MaxBac® kit), and such methods are well known in the art, as described in Summers and Smith, Texas Agricultural Experiment Station Bulletin No. 1555 (1987), incorporated herein by reference. As used herein, an insect cell capable of expressing a polynucleotide of the present invention is "transformed."

The protein of the invention may be prepared by culturing transformed host cells under culture conditions suitable to express the recombinant protein. The resulting expressed protein may then be purified from such culture (i.e., from culture medium or cell extracts) using known purification processes, such as gel filtration and ion exchange chromatography. The purification of the protein may also include an affinity column containing agents which will bind to the protein; one or more column steps over such affinity resins as concanavalin A-agarose, heparin-toyopearl® or Cibacrom blue 3GA

Sepharose®; one or more steps involving hydrophobic interaction chromatography using such resins as phenyl ether, butyl ether, or propyl ether; or immunoaffinity chromatography.

Alternatively, the protein of the invention may also be expressed in a form which will facilitate purification. For example, it may be expressed as a fusion protein, such as those of maltose binding protein (MBP), glutathione-S-transferase (GST) or thioredoxin (TRX). Kits for expression and purification of such fusion proteins are commercially available from New England BioLab (Beverly, MA), Pharmacia (Piscataway, NJ) and InVitrogen, respectively. The protein can also be tagged with an epitope and subsequently purified by using a specific antibody directed to such epitope. One such epitope ("Flag") is commercially available from Kodak (New Haven, CT).

Finally, one or more reverse-phase high performance liquid chromatography (RP-HPLC) steps employing hydrophobic RP-HPLC media, e.g., silica gel having pendant methyl or other aliphatic groups, can be employed to further purify the protein. Some or all of the foregoing purification steps, in various combinations, can also be employed to provide a substantially homogeneous isolated recombinant protein. The protein thus purified is substantially free of other mammalian proteins and is defined in accordance with the present invention as an "isolated protein."

The protein of the invention may also be expressed as a product of transgenic animals, e.g., as a component of the milk of transgenic cows, goats, pigs, or sheep which are characterized by somatic or germ cells containing a nucleotide sequence encoding the protein.

The protein may also be produced by known conventional chemical synthesis. Methods for constructing the proteins of the present invention by synthetic means are known to those skilled in the art. The synthetically-constructedprotein sequences, by virtue of sharing primary, secondary or tertiary structural and/or conformational characteristics with proteins may possess biological properties in common therewith, including protein activity. Thus, they may be employed as biologically active or immunological substitutes for natural, purified proteins in screening of therapeutic compounds and in immunological processes for the development of antibodies.

The proteins provided herein also include proteins characterized by amino acid sequences similar to those of purified proteins but into which modification are naturally provided or deliberately engineered. For example, modifications in the peptide or DNA sequences can be made by those skilled in the art using known techniques. Modifications

of interest in the protein sequences may include the alteration, substitution, replacement, insertion or deletion of a selected amino acid residue in the coding sequence. For example, one or more of the cysteine residues may be deleted or replaced with another amino acid to alter the conformation of the molecule. Techniques for such alteration, substitution, replacement, insertion or deletion are well known to those skilled in the art (see, e.g., U.S. Patent No. 4,518,584). Preferably, such alteration, substitution, replacement, insertion or deletion retains the desired activity of the protein.

Other fragments and derivatives of the sequences of proteins which would be expected to retain protein activity in whole or in part and may thus be useful for screening or other immunological methodologies may also be easily made by those skilled in the art given the disclosures herein. Such modifications are believed to be encompassed by the present invention.

USES AND BIOLOGICAL ACTIVITY

The polynucleotides and proteins of the present invention are expected to exhibit one or more of the uses or biological activities (including those associated with assays cited herein) identified below. Uses or activities described for proteins of the present invention may be provided by administration or use of such proteins or by administration or use of polynucleotides encoding such proteins (such as, for example, in gene therapies or vectors suitable for introduction of DNA).

Research Uses and Utilities

The polynucleotides provided by the present invention can be used by the research community for various purposes. The primary use of polynucleotides of the invention which are sESTs is as porbes for the identification and isolation of full-length cDNAs and genomic DNA molecules which correspond (i.e., is a longer polynucleotide sequence of which substantially the entire sEST is a fragment in the case of a full-length cDNA, or which encodes the sEST in the case of a genomic DNA molecule) to such sESTs. Techniques for use of such sequences as probes for larger cDNAs or genomic molecules are well known in the art.

The polynucleotides can also be used to express recombinant protein for analysis, characterization or therapeutic use; as markers for tissues in which the corresponding protein is preferentially expressed (either constitutively or at a particular stage of tissue differentiation or development or in disease states); as molecular weight markers on Southern gels; as chromosome markers or tags (when labeled) to identify chromosomes or to map related gene positions; to compare with endogenous DNA sequences in patients to identify potential genetic disorders; as probes to hybridize and thus discover novel, related DNA sequences; as a source of information to derive PCR primers for genetic fingerprinting; as a probe to "subtract-out" known sequences in the process of discovering other novel polynucleotides; for selecting and making oligomers for attachment to a "gene chip" or other support, including for examination of expression patterns; to raise anti-protein antibodies using DNA immunization techniques; and as an antigen to raise anti-DNA antibodies or elicit another immune response. Where the polynucleotide encodes a protein which binds or potentially binds to another protein (such as, for example, in a receptor-ligand interaction), the polynucleotide can also be used in interaction trap assays (such as, for example, that described in Gyuris et al., Cell 75:791-803 (1993)) to identify

polynucleotides encoding the other protein with which binding occurs or to identify inhibitors of the binding interaction.

The proteins provided by the present invention can similarly be used in assay to determine biological activity, including in a panel of multiple proteins for high-throughput screening; to raise antibodies or to elicit another immune response; as a reagent (including the labeled reagent) in assays designed to quantitatively determine levels of the protein (or its receptor) in biological fluids; as markers for tissues in which the corresponding protein is preferentially expressed (either constitutively or at a particular stage of tissue differentiation or development or in a disease state); and, of course, to isolate correlative receptors or ligands. Where the protein binds or potentially binds to another protein (such as, for example, in a receptor-ligand interaction), the protein can be used to identify the other protein with which binding occurs or to identify inhibitors of the binding interaction. Proteins involved in these binding interactions can also be used to screen for peptide or small molecule inhibitors or agonists of the binding interaction.

Any or all of these research utilities are capable of being developed into reagent grade or kit format for commercialization as research products.

Methods for performing the uses listed above are well known to those skilled in the art. References disclosing such methods include without limitation "Molecular Cloning: A Laboratory Manual", 2d ed., Cold Spring Harbor Laboratory Press, Sambrook, J., E.F. Fritsch and T. Maniatis eds., 1989, and "Methods in Enzymology: Guide to Molecular Cloning Techniques", Academic Press, Berger, S.L. and A.R. Kimmel eds., 1987.

Nutritional Uses

Polynucleotides and proteins of the present invention can also be used as nutritional sources or supplements. Such uses include without limitation use as a protein or amino acid supplement, use as a carbon source, use as a nitrogen source and use as a source of carbohydrate. In such cases the protein or polynucleotide of the invention can be added to the feed of a particular organism or can be administered as a separate solid or liquid preparation, such as in the form of powder, pills, solutions, suspensions or capsules. In the case of microorganisms, the protein or polynucleotide of the invention can be added to the medium in or on which the microorganism is cultured.

Cytokine and Cell Proliferation/Differentiation Activity

A protein of the present invention may exhibit cytokine, cell proliferation (either inducing or inhibiting) or cell differentiation (either inducing or inhibiting) activity or may induce production of other cytokines in certain cell populations. Many protein factors discovered to date, including all known cytokines, have exhibited activity in one or more factor dependent cell proliferation assays, and hence the assays serve as a convenient confirmation of cytokine activity. The activity of a protein of the present invention is evidenced by any one of a number of routine factor dependent cell proliferation assays for cell lines including, without limitation, 32D, DA2, DA1G, T10, B9, B9/11, BaF3, MC9/G, M+ (preB M+), 2E8, RB5, DA1, 123, T1165, HT2, CTLL2, TF-1, Mo7e and CMK.

The activity of a protein of the invention may, among other means, be measured by the following methods:

Assays for T-cell or thymocyte proliferation include without limitation those described in: Current Protocols in Immunology, Ed by J. E. Coligan, A.M. Kruisbeek, D.H. Margulies, E.M. Shevach, W Strober, Pub. Greene Publishing Associates and Wiley-Interscience (Chapter 3, In Vitro assays for Mouse Lymphocyte Function 3.1-3.19; Chapter 7, Immunologic studies in Humans); Takai et al., J. Immunol. 137:3494-3500, 1986; Bertagnolli et al., J. Immunol. 145:1706-1712, 1990; Bertagnolli et al., Cellular Immunology 133:327-341, 1991; Bertagnolli, et al., J. Immunol. 149:3778-3783, 1992; Bowman et al., J. Immunol. 152: 1756-1761, 1994.

Assays for cytokine production and/or proliferation of spleen cells, lymph node cells or thymocytes include, without limitation, those described in: Polyclonal T cell stimulation, Kruisbeek, A.M. and Shevach, E.M. In *Current Protocols in Immunology*. J.E.e.a. Coligan eds. Vol 1 pp. 3.12.1-3.12.14, John Wiley and Sons, Toronto. 1994; and Measurement of mouse and human Interferon γ, Schreiber, R.D. In *Current Protocols in Immunology*. J.E.e.a. Coligan eds. Vol 1 pp. 6.8.1-6.8.8, John Wiley and Sons, Toronto. 1994.

Assays for proliferation and differentiation of hematopoietic and lymphopoietic cells include, without limitation, those described in: Measurement of Human and Murine Interleukin 2 and Interleukin 4, Bottomly, K., Davis, L.S. and Lipsky, P.E. In *Current Protocols in Immunology*. J.E.e.a. Coligan eds. Vol 1 pp. 6.3.1-6.3.12, John Wiley and Sons, Toronto. 1991; deVries et al., J. Exp. Med. 173:1205-1211, 1991; Moreau et al., Nature 336:690-692, 1988; Greenberger et al., Proc. Natl. Acad. Sci. U.S.A. 80:2931-2938, 1983; Measurement of mouse and human interleukin 6 - Nordan, R. In *Current Protocols in Immunology*. J.E.e.a. Coligan eds. Vol 1 pp. 6.6.1-6.6.5, John Wiley

and Sons, Toronto. 1991; Smith et al., Proc. Natl. Acad. Sci. U.S.A. 83:1857-1861, 1986; Measurement of human Interleukin 11 - Bennett, F., Giannotti, J., Clark, S.C. and Turner, K. J. In *Current Protocols in Immunology*. J.E.e.a. Coligan eds. Vol 1 pp. 6.15.1 John Wiley and Sons, Toronto. 1991; Measurement of mouse and human Interleukin 9 - Ciarletta, A., Giannotti, J., Clark, S.C. and Turner, K.J. In *Current Protocols in Immunology*. J.E.e.a. Coligan eds. Vol 1 pp. 6.13.1, John Wiley and Sons, Toronto. 1991.

Assays for T-cell clone responses to antigens (which will identify, among others, proteins that affect APC-T cell interactions as well as direct T-cell effects by measuring proliferation and cytokine production) include, without limitation, those described in: Current Protocols in Immunology, Ed by J. E. Coligan, A.M. Kruisbeek, D.H. Margulies, E.M. Shevach, W Strober, Pub. Greene Publishing Associates and Wiley-Interscience (Chapter 3, In Vitro assays for Mouse Lymphocyte Function; Chapter 6, Cytokines and their cellular receptors; Chapter 7, Immunologic studies in Humans); Weinberger et al., Proc. Natl. Acad. Sci. USA 77:6091-6095, 1980; Weinberger et al., Eur. J. Immun. 11:405-411, 1981; Takai et al., J. Immunol. 137:3494-3500, 1986; Takai et al., J. Immunol. 140:508-512, 1988.

Immune Stimulating or Suppressing Activity

A protein of the present invention may also exhibit immune stimulating or immune suppressing activity, including without limitation the activities for which assays are described herein. A protein may be useful in the treatment of various immune deficiencies and disorders (including severe combined immunodeficiency (SCID)), e.g., in regulating (up or down) growth and proliferation of T and/or B lymphocytes, as well as effecting the cytolytic activity of NK cells and other cell populations. These immune deficiencies may be genetic or be caused by viral (e.g., HIV) as well as bacterial or fungal infections, or may result from autoimmune disorders. More specifically, infectious diseases causes by viral, bacterial, fungal or other infection may be treatable using a protein of the present invention, including infections by HIV, hepatitis viruses, herpesviruses, mycobacteria, Leishmania spp., malaria spp. and various fungal infections such as candidiasis. Of course, in this regard, a protein of the present invention may also be useful where a boost to the immune system generally may be desirable, *i.e.*, in the treatment of cancer.

Autoimmune disorders which may be treated using a protein of the present invention include, for example, connective tissue disease, multiple sclerosis, systemic lupus erythematosus, rheumatoid arthritis, autoimmune pulmonary inflammation, Guillain-Barre

syndrome, autoimmune thyroiditis, insulin dependent diabetes mellitis, myasthenia gravis, graft-versus-host disease and autoimmune inflammatory eye disease. Such a protein of the present invention may also to be useful in the treatment of allergic reactions and conditions, such as asthma (particularly allergic asthma) or other respiratory problems. Other conditions, in which immune suppression is desired (including, for example, organ transplantation), may also be treatable using a protein of the present invention.

Using the proteins of the invention it may also be possible to immune responses, in a number of ways. Down regulation may be in the form of inhibiting or blocking an immune response already in progress or may involve preventing the induction of an immune response. The functions of activated T cells may be inhibited by suppressing T cell responses or by inducing specific tolerance in T cells, or both. Immunosuppression of T cell responses is generally an active, non-antigen-specific, process which requires continuous exposure of the T cells to the suppressive agent. Tolerance, which involves inducing non-responsiveness or anergy in T cells, is distinguishable from immunosuppression in that it is generally antigen-specific and persists after exposure to the tolerizing agent has ceased. Operationally, tolerance can be demonstrated by the lack of a T cell response upon reexposure to specific antigen in the absence of the tolerizing agent.

Down regulating or preventing one or more antigen functions (including without limitation B lymphocyte antigen functions (such as , for example, B7)), *e.g.*, preventing high level lymphokine synthesis by activated T cells, will be useful in situations of tissue, skin and organ transplantation and in graft-versus-host disease (GVHD). For example, blockage of T cell function should result in reduced tissue destruction in tissue transplantation. Typically, in tissue transplants, rejection of the transplant is initiated through its recognition as foreign by T cells, followed by an immune reaction that destroys the transplant. The administration of a molecule which inhibits or blocks interaction of a B7 lymphocyte antigen with its natural ligand(s) on immune cells (such as a soluble, monomeric form of a peptide having B7-2 activity alone or in conjunction with a monomeric form of a peptide having an activity of another B lymphocyte antigen (*e.g.*, B7-1, B7-3) or blocking antibody), prior to transplantation can lead to the binding of the molecule to the natural ligand(s) on the immune cells without transmitting the corresponding costimulatory signal. Blocking B lymphocyte antigen function in this matter prevents cytokine synthesis by immune cells, such as T cells, and thus acts as an immunosuppressant Moreover, the lack of costimulation may also be sufficient to anergize the T cells, thereby inducing tolerance in a subject. Induction of long-term tolerance by B lymphocyte antigen-

blocking reagents may avoid the necessity of repeated administration of these blocking reagents. To achieve sufficient immunosuppression or tolerance in a subject, it may also be necessary to block the function of a combination of B lymphocyte antigens.

The efficacy of particular blocking reagents in preventing organ transplant rejection or GVHD can be assessed using animal models that are predictive of efficacy in humans. Examples of appropriate systems which can be used include allogeneic cardiac grafts in rats and xenogeneic pancreatic islet cell grafts in mice, both of which have been used to examine the immunosuppressive effects of CTLA4Ig fusion proteins *in vivo* as described in Lenschow *et al.*, Science *257*:789-792 (1992) and Turka *et al.*, Proc. Natl. Acad. Sci USA, *89*:11102-11105 (1992). In addition, murine models of GVHD (see Paul ed., Fundamental Immunology, Raven Press, New York, 1989, pp. 846-847) can be used to determine the effect of blocking B lymphocyte antigen function *in vivo* on the development of that disease.

Blocking antigen function may also be therapeutically useful for treating autoimmune diseases. Many autoimmune disorders are the result of inappropriate activation of T cells that are reactive against self tissue and which promote the production of cytokines and autoantibodies involved in the pathology of the diseases. Preventing the activation of autoreactive T cells may reduce or eliminate disease symptoms. Administration of reagents which block costimulation of T cells by disrupting receptor:ligand interactions of B lymphocyte antigens can be used to inhibit T cell activation and prevent production of autoantibodies or T cell-derived cytokines which may be involved in the disease process. Additionally, blocking reagents may induce antigen-specific tolerance of autoreactive T cells which could lead to long-term relief from the disease. The efficacy of blocking reagents in preventing or alleviating autoimmune disorders can be determined using a number of well-characterized animal models of human autoimmune diseases. Examples include murine experimental autoimmune encephalitis, systemic lupus erythmatosis in MRL/*lpr/lpr* mice or NZB hybrid mice, murine autoimmune collagen arthritis, diabetes mellitus in NOD mice and BB rats, and murine experimental myasthenia gravis (see Paul ed., Fundamental Immunology, Raven Press, New York, 1989, pp. 840-856).

Upregulation of an antigen function (preferably a B lymphocyte antigen function), as a means of up regulating immune responses, may also be useful in therapy. Upregulation of immune responses may be in the form of enhancing an existing immune response or eliciting an initial immune response. For example, enhancing an immune response through stimulating B lymphocyte antigen function may be useful in cases of viral

infection. In addition, systemic viral diseases such as influenza, the common cold, and encephalitis might be alleviated by the administration of stimulatory forms of B lymphocyte antigens systemically.

Alternatively, anti-viral immune responses may be enhanced in an infected patient by removing T cells from the patient, costimulating the T cells *in vitro* with viral antigen-pulsed APCs either expressing a peptide of the present invention or together with a stimulatory form of a soluble peptide of the present invention and reintroducing the *in vitro* activated T cells into the patient. Another method of enhancing anti-viral immune responses would be to isolate infected cells from a patient, transfect them with a nucleic acid encoding a protein of the present invention as described herein such that the cells express all or a portion of the protein on their surface, and reintroduce the transfected cells into the patient. The infected cells would now be capable of delivering a costimulatory signal to, and thereby activate, T cells *in vivo*.

In another application, up regulation or enhancement of antigen function (preferably B lymphocyte antigen function) may be useful in the induction of tumor immunity. Tumor cells (*e.g.*, sarcoma, melanoma, lymphoma, leukemia, neuroblastoma, carcinoma) transfected with a nucleic acid encoding at least one peptide of the present invention can be administered to a subject to overcome tumor-specific tolerance in the subject. If desired, the tumor cell can be transfected to express a combination of peptides. For example, tumor cells obtained from a patient can be transfected *ex vivo* with an expression vector directing the expression of a peptide having B7-2-like activity alone, or in conjunction with a peptide having B7-1-like activity and/or B7-3-like activity. The transfected tumor cells are returned to the patient to result in expression of the peptides on the surface of the transfected cell. Alternatively, gene therapy techniques can be used to target a tumor cell for transfection *in vivo*.

The presence of the peptide of the present invention having the activity of a B lymphocyte antigen(s) on the surface of the tumor cell provides the necessary costimulation signal to T cells to induce a T cell mediated immune response against the transfected tumor cells. In addition, tumor cells which lack MHC class I or MHC class II molecules, or which fail to reexpress sufficient amounts of MHC class I or MHC class II molecules, can be transfected with nucleic acid encoding all or a portion of (*e.g.*, a cytoplasmic-domain truncated portion) of an MHC class I α chain protein and β_2 microglobulin protein or an MHC class II α chain protein and an MHC class II β chain protein to thereby express MHC class I or MHC class II proteins on the cell surface. Expression of the appropriate class I

or class II MHC in conjunction with a peptide having the activity of a B lymphocyte antigen (*e.g.*,B7-1, B7-2, B7-3) induces a T cell mediated immune response against the transfected tumor cell. Optionally, a gene encoding an antisense construct which blocks expression of an MHC class II associated protein, such as the invariant chain, can also be cotransfected with a DNA encoding a peptide having the activity of a B lymphocyte antigen to promote presentation of tumor associated antigens and induce tumor specific immunity. Thus, the induction of a T cell mediated immune response in a human subject may be sufficient to overcome tumor-specific tolerance in the subject.

The activity of a protein of the invention may, among other means, be measured by the following methods:

Suitable assays for thymocyte or splenocyte cytotoxicity include, without limitation, those described in: Current Protocols in Immunology, Ed by J. E. Coligan, A.M. Kruisbeek, D.H. Margulies, E.M. Shevach, W Strober, Pub. Greene Publishing Associates and Wiley-Interscience (Chapter 3, In Vitro assays for Mouse Lymphocyte Function 3.1-3.19; Chapter 7, Immunologic studies in Humans); Herrmann et al., Proc. Natl. Acad. Sci. USA 78:2488-2492, 1981; Herrmann et al., J. Immunol. 128:1968-1974, 1982; Handa et al., J. Immunol. 135:1564-1572, 1985; Takai et al., J. Immunol. 137:3494-3500, 1986; Takai et al., J. Immunol. 140:508-512, 1988; Herrmann et al., Proc. Natl. Acad. Sci. USA 78:2488-2492, 1981; Herrmann et al., J. Immunol. 128:1968-1974, 1982; Handa et al., J. Immunol. 135:1564-1572, 1985; Takai et al., J. Immunol. 137:3494-3500, 1986; Bowmanet al., J. Virology 61:1992-1998; Takai et al., J. Immunol. 140:508-512, 1988; Bertagnolli et al., Cellular Immunology 133:327-341, 1991; Brown et al., J. Immunol. 153:3079-3092, 1994.

Assays for T-cell-dependent immunoglobulin responses and isotype switching (which will identify, among others, proteins that modulate T-cell dependent antibody responses and that affect Th1/Th2 profiles) include, without limitation, those described in: Maliszewski, J. Immunol. 144:3028-3033, 1990; and Assays for B cell function: *In vitro* antibody production, Mond, J.J. and Brunswick, M. In *Current Protocols in Immunology*. J.E.e.a. Coligan eds. Vol 1 pp. 3.8.1-3.8.16, John Wiley and Sons, Toronto. 1994.

Mixed lymphocyte reaction (MLR) assays (which will identify, among others, proteins that generate predominantly Th1 and CTL responses) include, without limitation, those described in: Current Protocols in Immunology, Ed by J. E. Coligan, A.M. Kruisbeek, D.H. Margulies, E.M. Shevach, W Strober, Pub. Greene Publishing Associates and Wiley-Interscience (Chapter 3, In Vitro assays for Mouse Lymphocyte Function 3.1-

3.19; Chapter 7, Immunologic studies in Humans); Takai et al., J. Immunol. 137:3494-3500, 1986; Takai et al., J. Immunol. 140:508-512, 1988; Bertagnolli et al., J. Immunol. 149:3778-3783, 1992.

Dendritic cell-dependent assays (which will identify, among others, proteins expressed by dendritic cells that activate naive T-cells) include, without limitation, those described in: Guery et al., J. Immunol. 134:536-544, 1995; Inaba et al., Journal of Experimental Medicine 173:549-559, 1991; Macatonia et al., Journal of Immunology 154:5071-5079, 1995; Porgador et al., Journal of Experimental Medicine 182:255-260, 1995; Nair et al., Journal of Virology 67:4062-4069, 1993; Huang et al., Science 264:961-965, 1994; Macatonia et al., Journal of Experimental Medicine 169:1255-1264, 1989; Bhardwaj et al., Journal of Clinical Investigation 94:797-807, 1994; and Inaba et al., Journal of Experimental Medicine 172:631-640, 1990.

Assays for lymphocyte survival/apoptosis (which will identify, among others, proteins that prevent apoptosis after superantigen induction and proteins that regulate lymphocyte homeostasis) include, without limitation, those described in: Darzynkiewicz et al., Cytometry 13:795-808, 1992; Gorczyca et al., Leukemia 7:659-670, 1993; Gorczyca et al., Cancer Research 53:1945-1951, 1993; Itoh et al., Cell 66:233-243, 1991; Zacharchuk, Journal of Immunology 145:4037-4045, 1990; Zamai et al., Cytometry 14:891-897, 1993; Gorczyca et al., International Journal of Oncology 1:639-648, 1992.

Assays for proteins that influence early steps of T-cell commitment and development include, without limitation, those described in: Antica et al., Blood 84:111-117, 1994; Fine et al., Cellular Immunology 155:111-122, 1994; Galy et al., Blood 85:2770-2778, 1995; Toki et al., Proc. Nat. Acad Sci. USA 88:7548-7551, 1991.

Hematopoiesis Regulating Activity

A protein of the present invention may be useful in regulation of hematopoiesis and, consequently, in the treatment of myeloid or lymphoid cell deficiencies. Even marginal biological activity in support of colony forming cells or of factor-dependent cell lines indicates involvement in regulating hematopoiesis, e.g. in supporting the growth and proliferation of erythroid progenitor cells alone or in combination with other cytokines, thereby indicating utility, for example, in treating various anemias or for use in conjunction with irradiation/chemotherapy to stimulate the production of erythroid precursors and/or erythroid cells; in supporting the growth and proliferation of myeloid cells such as granulocytes and monocytes/macrophages (i.e., traditional CSF activity) useful, for

example, in conjunction with chemotherapy to prevent or treat consequent myelo-suppression; in supporting the growth and proliferation of megakaryocytes and consequently of platelets thereby allowing prevention or treatment of various platelet disorders such as thrombocytopenia, and generally for use in place of or complimentary to platelet transfusions; and/or in supporting the growth and proliferation of hematopoietic stem cells which are capable of maturing to any and all of the above-mentioned hematopoietic cells and therefore find therapeutic utility in various stem cell disorders (such as those usually treated with transplantation, including, without limitation, aplastic anemia and paroxysmal nocturnal hemoglobinuria), as well as in repopulating the stem cell compartment post irradiation/chemotherapy, either *in-vivo* or *ex-vivo* (i.e., in conjunction with bone marrow transplantation or with peripheral progenitor cell transplantation (homologous or heterologous)) as normal cells or genetically manipulated for gene therapy.

The activity of a protein of the invention may, among other means, be measured by the following methods:

Suitable assays for proliferation and differentiation of various hematopoietic lines are cited above.

Assays for embryonic stem cell differentiation (which will identify, among others, proteins that influence embryonic differentiation hematopoiesis) include, without limitation, those described in: Johansson et al. Cellular Biology 15:141-151, 1995; Keller et al., Molecular and Cellular Biology 13:473-486, 1993; McClanahan et al., Blood 81:2903-2915, 1993.

Assays for stem cell survival and differentiation (which will identify, among others, proteins that regulate lympho-hematopoiesis) include, without limitation, those described in: Methylcellulose colony forming assays, Freshney, M.G. In *Culture of Hematopoietic Cells*. R.I. Freshney, *et al.* eds. Vol pp. 265-268, Wiley-Liss, Inc., New York, NY. 1994; Hirayama et al., Proc. Natl. Acad. Sci. USA 89:5907-5911, 1992; Primitive hematopoietic colony forming cells with high proliferative potential, McNiece, I.K. and Briddell, R.A. In *Culture of Hematopoietic Cells*. R.I. Freshney, *et al.* eds. Vol pp. 23-39, Wiley-Liss, Inc., New York, NY. 1994; Neben et al., Experimental Hematology 22:353-359, 1994; Cobblestone area forming cell assay, Ploemacher, R.E. In *Culture of Hematopoietic Cells*. R.I. Freshney, *et al.* eds. Vol pp. 1-21, Wiley-Liss, Inc.., New York, NY. 1994; Long term bone marrow cultures in the presence of stromal cells, Spooncer, E., Dexter, M. and Allen, T. In *Culture of Hematopoietic Cells*. R.I. Freshney, *et al.* eds. Vol pp. 163-179, Wiley-Liss, Inc., New York, NY. 1994; Long term culture initiating cell assay, Sutherland,

H.J. In *Culture of Hematopoietic Cells*. R.I. Freshney, *et al.* eds. Vol pp. 139-162, Wiley-Liss, Inc., New York, NY. 1994.

Tissue Growth Activity

A protein of the present invention also may have utility in compositions used for bone, cartilage, tendon, ligament and/or nerve tissue growth or regeneration, as well as for wound healing and tissue repair and replacement, and in the treatment of burns, incisions and ulcers.

A protein of the present invention, which induces cartilage and/or bone growth in circumstances where bone is not normally formed, has application in the healing of bone fractures and cartilage damage or defects in humans and other animals. Such a preparation employing a protein of the invention may have prophylactic use in closed as well as open fracture reduction and also in the improved fixation of artificial joints. *De novo* bone formation induced by an osteogenic agent contributes to the repair of congenital, trauma induced, or oncologic resection induced craniofacial defects, and also is useful in cosmetic plastic surgery.

A protein of this invention may also be used in the treatment of periodontal disease, and in other tooth repair processes. Such agents may provide an environment to attract bone-forming cells, stimulate growth of bone-forming cells or induce differentiation of progenitors of bone-forming cells. A protein of the invention may also be useful in the treatment of osteoporosis or osteoarthritis, such as through stimulation of bone and/or cartilage repair or by blocking inflammation or processes of tissue destruction (collagenase activity, osteoclast activity, etc.) mediated by inflammatory processes.

Another category of tissue regeneration activity that may be attributable to the protein of the present invention is tendon/ligament formation. A protein of the present invention, which induces tendon/ligament-like tissue or other tissue formation in circumstances where such tissue is not normally formed, has application in the healing of tendon or ligament tears, deformities and other tendon or ligament defects in humans and other animals. Such a preparation employing a tendon/ligament-liketissue inducing protein may have prophylactic use in preventing damage to tendon or ligament tissue, as well as use in the improved fixation of tendon or ligament to bone or other tissues, and in repairing defects to tendon or ligament tissue. De novo tendon/ligament-liketissue formation induced by a composition of the present invention contributes to the repair of congenital, trauma induced, or other tendon or ligament defects of other origin, and is also useful in cosmetic

plastic surgery for attachment or repair of tendons or ligaments. The compositions of the present invention may provide an environment to attract tendon- or ligament-forming cells, stimulate growth of tendon- or ligament-forming cells, induce differentiation of progenitors of tendon- or ligament-forming cells, or induce growth of tendon/ligament cells or progenitors *ex vivo* for return *in vivo* to effect tissue repair. The compositions of the invention may also be useful in the treatment of tendinitis, carpal tunnel syndrome and other tendon or ligament defects. The compositions may also include an appropriate matrix and/or sequestering agent as a carrier as is well known in the art.

The protein of the present invention may also be useful for proliferation of neural cells and for regeneration of nerve and brain tissue, *i.e.* for the treatment of central and peripheral nervous system diseases and neuropathies, as well as mechanical and traumatic disorders, which involve degeneration, death or trauma to neural cells or nerve tissue. More specifically, a protein may be used in the treatment of diseases of the peripheral nervous system, such as peripheral nerve injuries, peripheral neuropathy and localized neuropathies, and central nervous system diseases, such as Alzheimer's, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis, and Shy-Drager syndrome. Further conditions which may be treated in accordance with the present invention include mechanical and traumatic disorders, such as spinal cord disorders, head trauma and cerebrovascular diseases such as stroke. Peripheral neuropathies resulting from chemotherapy or other medical therapies may also be treatable using a protein of the invention.

Proteins of the invention may also be useful to promote better or faster closure of non-healing wounds, including without limitation pressure ulcers, ulcers associated with vascular insufficiency, surgical and traumatic wounds, and the like.

It is expected that a protein of the present invention may also exhibit activity for generation or regeneration of other tissues, such as organs (including, for example, pancreas, liver, intestine, kidney, skin, endothelium), muscle (smooth, skeletal or cardiac) and vascular (including vascular endothelium) tissue, or for promoting the growth of cells comprising such tissues. Part of the desired effects may be by inhibition or modulation of fibrotic scarring to allow normal tissue to regenerate. A protein of the invention may also exhibit angiogenic activity.

A protein of the present invention may also be useful for gut protection or regeneration and treatment of lung or liver fibrosis, reperfusion injury in various tissues, and conditions resulting from systemic cytokine damage.

A protein of the present invention may also be useful for promoting or inhibiting differentiation of tissues described above from precursor tissues or cells; or for inhibiting the growth of tissues described above.

The activity of a protein of the invention may, among other means, be measured by the following methods:

Assays for tissue generation activity include, without limitation, those described in: International Patent Publication No. WO95/16035 (bone, cartilage, tendon); International Patent Publication No. WO95/05846 (nerve, neuronal); International Patent Publication No. WO91/07491 (skin, endothelium).

Assays for wound healing activity include, without limitation, those described in: Winter, Epidermal Wound Healing, pps. 71-112 (Maibach, HI and Rovee, DT, eds.), Year Book Medical Publishers, Inc., Chicago, as modified by Eaglstein and Mertz, J. Invest. Dermatol 71:382-84 (1978).

Activin/Inhibin Activity

A protein of the present invention may also exhibit activin- or inhibin-related activities. Inhibins are characterized by their ability to inhibit the release of follicle stimulating hormone (FSH), while activins and are characterized by their ability to stimulate the release of follicle stimulating hormone (FSH). Thus, a protein of the present invention, alone or in heterodimers with a member of the inhibin α family, may be useful as a contraceptive based on the ability of inhibins to decrease fertility in female mammals and decrease spermatogenesis in male mammals. Administration of sufficient amounts of other inhibins can induce infertility in these mammals. Alternatively, the protein of the invention, as a homodimer or as a heterodimer with other protein subunits of the inhibin-β group, may be useful as a fertility inducing therapeutic, based upon the ability of activin molecules in stimulating FSH release from cells of the anterior pituitary. See, for example, United States Patent 4,798,885. A protein of the invention may also be useful for advancement of the onset of fertility in sexually immature mammals, so as to increase the lifetime reproductive performance of domestic animals such as cows, sheep and pigs.

The activity of a protein of the invention may, among other means, be measured by the following methods:

Assays for activin/inhibin activity include, without limitation, those described in: Vale et al., Endocrinology 91:562-572, 1972; Ling et al., Nature 321:779-782, 1986; Vale

et al., Nature 321:776-779, 1986; Mason et al., Nature 318:659-663, 1985; Forage et al., Proc. Natl. Acad. Sci. USA 83:3091-3095, 1986.

Chemotactic/Chemokinetic Activity

A protein of the present invention may have chemotactic or chemokinetic activity (e.g., act as a chemokine) for mammalian cells, including, for example, monocytes, fibroblasts, neutrophils, T-cells, mast cells, eosinophils, epithelial and/or endothelial cells. Chemotactic and chemokinetic proteins can be used to mobilize or attract a desired cell population to a desired site of action. Chemotactic or chemokinetic proteins provide particular advantages in treatment of wounds and other trauma to tissues, as well as in treatment of localized infections. For example, attraction of lymphocytes, monocytes or neutrophils to tumors or sites of infection may result in improved immune responses against the tumor or infecting agent.

A protein or peptide has chemotactic activity for a particular cell population if it can stimulate, directly or indirectly, the directed orientation or movement of such cell population. Preferably, the protein or peptide has the ability to directly stimulate directed movement of cells. Whether a particular protein has chemotactic activity for a population of cells can be readily determined by employing such protein or peptide in any known assay for cell chemotaxis.

The activity of a protein of the invention may, among other means, be measured by the following methods:

Assays for chemotactic activity (which will identify proteins that induce or prevent chemotaxis) consist of assays that measure the ability of a protein to induce the migration of cells across a membrane as well as the ability of a protein to induce the adhesion of one cell population to another cell population. Suitable assays for movement and adhesion include, without limitation, those described in: Current Protocols in Immunology, Ed by J.E. Coligan, A.M. Kruisbeek, D.H. Margulies, E.M. Shevach, W.Strober, Pub. Greene Publishing Associates and Wiley-Interscience (Chapter 6.12, Measurement of alpha and beta Chemokines 6.12.1-6.12.28; Taub et al. J. Clin. Invest. 95:1370-1376, 1995; Lind et al. APMIS 103:140-146, 1995; Muller et al Eur. J. Immunol. 25: 1744-1748; Gruber et al. J. of Immunol. 152:5860-5867, 1994; Johnston et al. J. of Immunol. 153: 1762-1768, 1994.

Hemostatic and Thrombolytic Activity

A protein of the invention may also exhibit hemostatic or thrombolytic activity. As a result, such a protein is expected to be useful in treatment of various coagulation disorders (including hereditary disorders, such as hemophilias) or to enhance coagulation and other hemostatic events in treating wounds resulting from trauma, surgery or other causes. A protein of the invention may also be useful for dissolving or inhibiting formation of thromboses and for treatment and prevention of conditions resulting therefrom (such as, for example, infarction of cardiac and central nervous system vessels (e.g., stroke).

The activity of a protein of the invention may, among other means, be measured by the following methods:

Assay for hemostatic and thrombolytic activity include, without limitation, those described in: Linet et al., J. Clin. Pharmacol. 26:131-140, 1986; Burdick et al., Thrombosis Res. 45:413-419, 1987; Humphrey et al., Fibrinolysis 5:71-79 (1991); Schaub, Prostaglandins 35:467-474, 1988.

Receptor/Ligand Activity

A protein of the present invention may also demonstrate activity as receptors, receptor ligands or inhibitors or agonists of receptor/ligand interactions. Examples of such receptors and ligands include, without limitation, cytokine receptors and their ligands, receptor kinases and their ligands, receptor phosphatases and their ligands, receptors involved in cell-cell interactions and their ligands (including without limitation, cellular adhesion molecules (such as selectins, integrins and their ligands) and receptor/ligand pairs involved in antigen presentation, antigen recognition and development of cellular and humoral immune responses). Receptors and ligands are also useful for screening of potential peptide or small molecule inhibitors of the relevant receptor/ligand interaction. A protein of the present invention (including, without limitation, fragments of receptors and ligands) may themselves be useful as inhibitors of receptor/ligand interactions.

The activity of a protein of the invention may, among other means, be measured by the following methods:

Suitable assays for receptor-ligand activity include without limitation those described in:Current Protocols in Immunology, Ed by J.E. Coligan, A.M. Kruisbeek, D.H. Margulies, E.M. Shevach, W.Strober, Pub. Greene Publishing Associates and Wiley-Interscience (Chapter 7.28, Measurement of Cellular Adhesion under static conditions 7.28.1-7.28.22), Takai et al., Proc. Natl. Acad. Sci. USA 84:6864-6868, 1987; Bierer et al., J. Exp. Med. 168:1145-1156, 1988; Rosenstein et al., J. Exp. Med.

169:149-160 1989; Stoltenborg et al., J. Immunol. Methods 175:59-68, 1994; Stitt et al., Cell 80:661-670, 1995.

Anti-Inflammatory Activity

Proteins of the present invention may also exhibit anti-inflammatory activity. The anti-inflammatory activity may be achieved by providing a stimulus to cells involved in the inflammatory response, by inhibiting or promoting cell-cell interactions (such as, for example, cell adhesion), by inhibiting or promoting chemotaxis of cells involved in the inflammatory process, inhibiting or promoting cell extravasation, or by stimulating or suppressing production of other factors which more directly inhibit or promote an inflammatory response. Proteins exhibiting such activities can be used to treat inflammatory conditions including chronic or acute conditions), including without limitation inflammation associated with infection (such as septic shock, sepsis or systemic inflammatory response syndrome (SIRS)), ischemia-reperfusion injury, endotoxin lethality, arthritis, complement-mediated hyperacute rejection, nephritis, cytokine or chemokine-induced lung injury, inflammatory bowel disease, Crohn's disease or resulting from over production of cytokines such as TNF or IL-1. Proteins of the invention may also be useful to treat anaphylaxis and hypersensitivity to an antigenic substance or material.

Tumor Inhibition Activity

In addition to the activities described above for immunological treatment or prevention of tumors, a protein of the invention may exhibit other anti-tumor activities. A protein may inhibit tumor growth directly or indirectly (such as, for example, via ADCC). A protein may exhibit its tumor inhibitory activity by acting on tumor tissue or tumor precursor tissue, by inhibiting formation of tissues necessary to support tumor growth (such as, for example, by inhibiting angiogenesis), by causing production of other factors, agents or cell types which inhibit tumor growth, or by suppressing, eliminating or inhibiting factors, agents or cell types which promote tumor growth.

Other Activities

A protein of the invention may also exhibit one or more of the following additional activities or effects: inhibiting the growth, infection or function of, or killing, infectious agents, including, without limitation, bacteria, viruses, fungi and other parasites; effecting

(suppressing or enhancing) bodily characteristics, including, without limitation, height, weight, hair color, eye color, skin, fat to lean ratio or other tissue pigmentation, or organ or body part size or shape (such as, for example, breast augmentation or diminution, change in bone form or shape); effecting biorhythms or caricadic cycles or rhythms; effecting the fertility of male or female subjects; effecting the metabolism, catabolism, anabolism, processing, utilization, storage or elimination of dietary fat, lipid, protein, carbohydrate, vitamins, minerals, cofactors or other nutritional factors or component(s); effecting behavioral characteristics, including, without limitation, appetite, libido, stress, cognition (including cognitive disorders), depression (including depressive disorders) and violent behaviors; providing analgesic effects or other pain reducing effects; promoting differentiation and growth of embryonic stem cells in lineages other than hematopoietic lineages; hormonal or endocrine activity; in the case of enzymes, correcting deficiencies of the enzyme and treating deficiency-related diseases; treatment of hyperproliferative disorders (such as, for example, psoriasis); immunoglobulin-like activity (such as, for example, the ability to bind antigens or complement); and the ability to act as an antigen in a vaccine composition to raise an immune response against such protein or another material or entity which is cross-reactive with such protein.

ADMINISTRATION AND DOSING

A protein of the present invention (from whatever source derived, including without limitation from recombinant and non-recombinant sources) may be used in a pharmaceutical composition when combined with a pharmaceutically acceptable carrier. Such a composition may also contain (in addition to protein and a carrier) diluents, fillers, salts, buffers, stabilizers, solubilizers, and other materials well known in the art. The term "pharmaceutically acceptable" means a non-toxic material that does not interfere with the effectiveness of the biological activity of the active ingredient(s). The characteristics of the carrier will depend on the route of administration. The pharmaceutical composition of the invention may also contain cytokines, lymphokines, or other hematopoietic factors such as M-CSF, GM-CSF, TNF, IL-1, IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, IL-10, IL-11, IL-12, IL-13, IL-14, IL-15, IFN, TNF0, TNF1, TNF2, G-CSF, Meg-CSF, thrombopoietin, stem cell factor, and erythropoietin. The pharmaceutical composition may further contain other agents which either enhance the activity of the protein or compliment its activity or use in treatment. Such additional factors and/or agents may be included in the pharmaceutical composition to produce a synergistic effect with protein of the invention, or to minimize side effects. Conversely, protein of the present invention may be included in formulations of the particular cytokine, lymphokine, other hematopoietic factor, thrombolytic or anti-thrombotic factor, or anti-inflammatory agent to minimize side effects of the cytokine, lymphokine, other hematopoietic factor, thrombolytic or anti-thrombotic factor, or anti-inflammatory agent.

A protein of the present invention may be active in multimers (e.g., heterodimers or homodimers) or complexes with itself or other proteins. As a result, pharmaceutical compositions of the invention may comprise a protein of the invention in such multimeric or complexed form.

The pharmaceutical composition of the invention may be in the form of a complex of the protein(s) of present invention along with protein or peptide antigens. The protein and/or peptide antigen will deliver a stimulatory signal to both B and T lymphocytes. B lymphocytes will respond to antigen through their surface immunoglobulin receptor. T lymphocytes will respond to antigen through the T cell receptor (TCR) following presentation of the antigen by MHC proteins. MHC and structurally related proteins including those encoded by class I and class II MHC genes on host cells will serve to present the peptide antigen(s) to T lymphocytes. The antigen components could also be supplied as purified MHC-peptide complexes alone or with co-stimulatory molecules that

can directly signal T cells. Alternatively antibodies able to bind surface immunolgobulin and other molecules on B cells as well as antibodies able to bind the TCR and other molecules on T cells can be combined with the pharmaceutical composition of the invention.

The pharmaceutical composition of the invention may be in the form of a liposome in which protein of the present invention is combined, in addition to other pharmaceutically acceptable carriers, with amphipathic agents such as lipids which exist in aggregated form as micelles, insoluble monolayers, liquid crystals, or lamellar layers in aqueous solution. Suitable lipids for liposomal formulation include, without limitation, monoglycerides, diglycerides, sulfatides, lysolecithin, phospholipids, saponin, bile acids, and the like. Preparation of such liposomal formulations is within the level of skill in the art, as disclosed, for example, in U.S. Patent No. 4,235,871; U.S. Patent No. 4,501,728; U.S. Patent No. 4,837,028; and U.S. Patent No. 4,737,323, all of which are incorporated herein by reference.

As used herein, the term "therapeutically effective amount" means the total amount of each active component of the pharmaceutical composition or method that is sufficient to show a meaningful patient benefit, i.e., treatment, healing, prevention or amelioration of the relevant medical condition, or an increase in rate of treatment, healing, prevention or amelioration of such conditions. When applied to an individual active ingredient, administered alone, the term refers to that ingredient alone. When applied to a combination, the term refers to combined amounts of the active ingredients that result in the therapeutic effect, whether administered in combination, serially or simultaneously.

In practicing the method of treatment or use of the present invention, a therapeutically effective amount of protein of the present invention is administered to a mammal having a condition to be treated. Protein of the present invention may be administered in accordance with the method of the invention either alone or in combination with other therapies such as treatments employing cytokines, lymphokines or other hematopoietic factors. When co-administered with one or more cytokines, lymphokines or other hematopoietic factors, protein of the present invention may be administered either simultaneously with the cytokine(s), lymphokine(s), other hematopoietic factor(s), thrombolytic or anti-thrombotic factors, or sequentially. If administered sequentially, the attending physician will decide on the appropriate sequence of administering protein of the present invention in combination with cytokine(s), lymphokine(s), other hematopoietic factor(s), thrombolytic or anti-thrombotic factors.

Administration of protein of the present invention used in the pharmaceutical composition or to practice the method of the present invention can be carried out in a variety of conventional ways, such as oral ingestion, inhalation, topical application or cutaneous, subcutaneous, intraperitoneal, parenteral or intravenous injection. Intravenous administration to the patient is preferred.

When a therapeutically effective amount of protein of the present invention is administered orally, protein of the present invention will be in the form of a tablet, capsule, powder, solution or elixir. When administered in tablet form, the pharmaceutical composition of the invention may additionally contain a solid carrier such as a gelatin or an adjuvant. The tablet, capsule, and powder contain from about 5 to 95% protein of the present invention, and preferably from about 25 to 90% protein of the present invention. When administered in liquid form, a liquid carrier such as water, petroleum, oils of animal or plant origin such as peanut oil, mineral oil, soybean oil, or sesame oil, or synthetic oils may be added. The liquid form of the pharmaceutical composition may further contain physiological saline solution, dextrose or other saccharide solution, or glycols such as ethylene glycol, propylene glycol or polyethylene glycol. When administered in liquid form, the pharmaceutical composition contains from about 0.5 to 90% by weight of protein of the present invention, and preferably from about 1 to 50% protein of the present invention.

When a therapeutically effective amount of protein of the present invention is administered by intravenous, cutaneous or subcutaneous injection, protein of the present invention will be in the form of a pyrogen-free, parenterally acceptable aqueous solution. The preparation of such parenterally acceptable protein solutions, having due regard to pH, isotonicity, stability, and the like, is within the skill in the art. A preferred pharmaceutical composition for intravenous, cutaneous, or subcutaneous injection should contain, in addition to protein of the present invention, an isotonic vehicle such as Sodium Chloride Injection, Ringer's Injection, Dextrose Injection, Dextrose and Sodium Chloride Injection, Lactated Ringer's Injection, or other vehicle as known in the art. The pharmaceutical composition of the present invention may also contain stabilizers, preservatives, buffers, antioxidants, or other additives known to those of skill in the art.

The amount of protein of the present invention in the pharmaceutical composition of the present invention will depend upon the nature and severity of the condition being treated, and on the nature of prior treatments which the patient has undergone. Ultimately, the attending physician will decide the amount of protein of the present invention with

which to treat each individual patient. Initially, the attending physician will administer low doses of protein of the present invention and observe the patient's response. Larger doses of protein of the present invention may be administered until the optimal therapeutic effect is obtained for the patient, and at that point the dosage is not increased further. It is contemplated that the various pharmaceutical compositions used to practice the method of the present invention should contain about 0.01 μg to about 100 mg (preferably about 0.1ng to about 10 mg, more preferably about 0.1 μg to about 1 mg) of protein of the present invention per kg body weight.

The duration of intravenous therapy using the pharmaceutical composition of the present invention will vary, depending on the severity of the disease being treated and the condition and potential idiosyncratic response of each individual patient. It is contemplated that the duration of each application of the protein of the present invention will be in the range of 12 to 24 hours of continuous intravenous administration. Ultimately the attending physician will decide on the appropriate duration of intravenous therapy using the pharmaceutical composition of the present invention.

Protein of the invention may also be used to immunize animals to obtain polyclonal and monoclonal antibodies which specifically react with the protein. Such antibodies may be obtained using either the entire protein or fragments thereof as an immunogen. The peptide immunogens additionally may contain a cysteine residue at the carboxyl terminus, and are conjugated to a hapten such as keyhole limpet hemocyanin (KLH). Methods for synthesizing such peptides are known in the art, for example, as in R.P. Merrifield, J. Amer.Chem. Soc. 85, 2149-2154 (1963); J.L. Krstenansky, *et al.*, FEBS Lett. 211, 10 (1987). Monoclonal antibodies binding to the protein of the invention may be useful diagnostic agents for the immunodetection of the protein. Neutralizing monoclonal antibodies binding to the protein may also be useful therapeutics for both conditions associated with the protein and also in the treatment of some forms of cancer where abnormal expression of the protein is involved. In the case of cancerous cells or leukemic cells, neutralizing monoclonal antibodies against the protein may be useful in detecting and preventing the metastatic spread of the cancerous cells, which may be mediated by the protein.

For compositions of the present invention which are useful for bone, cartilage, tendon or ligament regeneration, the therapeutic method includes administering the composition topically, systematically, or locally as an implant or device. When administered, the therapeutic composition for use in this invention is, of course, in a

pyrogen-free, physiologically acceptable form. Further, the composition may desirably be encapsulated or injected in a viscous form for delivery to the site of bone, cartilage or tissue damage. Topical administration may be suitable for wound healing and tissue repair. Therapeutically useful agents other than a protein of the invention which may also optionally be included in the composition as described above, may alternatively or additionally, be administered simultaneously or sequentially with the composition in the methods of the invention. Preferably for bone and/or cartilage formation, the composition would include a matrix capable of delivering the protein-containing composition to the site of bone and/or cartilage damage, providing a structure for the developing bone and cartilage and optimally capable of being resorbed into the body. Such matrices may be formed of materials presently in use for other implanted medical applications.

The choice of matrix material is based on biocompatibility, biodegradability, mechanical properties, cosmetic appearance and interface properties. The particular application of the compositions will define the appropriate formulation. Potential matrices for the compositions may be biodegradable and chemically defined calcium sulfate, tricalciumphosphate, hydroxyapatite, polylactic acid, polyglycolic acid and polyanhydrides. Other potential materials are biodegradable and biologically well-defined, such as bone or dermal collagen. Further matrices are comprised of pure proteins or extracellular matrix components. Other potential matrices are nonbiodegradable and chemically defined, such as sintered hydroxapatite, bioglass, aluminates, or other ceramics. Matrices may be comprised of combinations of any of the above mentioned types of material, such as polylactic acid and hydroxyapatite or collagen and tricalciumphosphate. The bioceramics may be altered in composition, such as in calcium-aluminate-phosphate and processing to alter pore size, particle size, particle shape, and biodegradability.

Presently preferred is a 50:50 (mole weight) copolymer of lactic acid and glycolic acid in the form of porous particles having diameters ranging from 150 to 800 microns. In some applications, it will be useful to utilize a sequestering agent, such as carboxymethyl cellulose or autologous blood clot, to prevent the protein compositions from disassociating from the matrix.

A preferred family of sequestering agents is cellulosic materials such as alkylcelluloses (including hydroxyalkylcelluloses), including methylcellulose, ethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, hydroxypropyl-methylcellulose, and carboxymethylcellulose, the most preferred being cationic salts of carboxymethylcellulose (CMC). Other preferred sequestering agents include hyaluronic acid, sodium alginate,

poly(ethylene glycol), polyoxyethylene oxide, carboxyvinyl polymer and poly(vinyl alcohol). The amount of sequestering agent useful herein is 0.5-20 wt%, preferably 1-10 wt% based on total formulation weight, which represents the amount necessary to prevent desorbtion of the protein from the polymer matrix and to provide appropriate handling of the composition, yet not so much that the progenitor cells are prevented from infiltrating the matrix, thereby providing the protein the opportunity to assist the osteogenic activity of the progenitor cells.

In further compositions, proteins of the invention may be combined with other agents beneficial to the treatment of the bone and/or cartilage defect, wound, or tissue in question. These agents include various growth factors such as epidermal growth factor (EGF), platelet derived growth factor (PDGF), transforming growth factors (TGF-α and TGF-β), and insulin-like growth factor (IGF).

The therapeutic compositions are also presently valuable for veterinary applications. Particularly domestic animals and thoroughbred horses, in addition to humans, are desired patients for such treatment with proteins of the present invention.

The dosage regimen of a protein-containing pharmaceutical composition to be used in tissue regeneration will be determined by the attending physician considering various factors which modify the action of the proteins, e.g., amount of tissue weight desired to be formed, the site of damage, the condition of the damaged tissue, the size of a wound, type of damaged tissue (e.g., bone), the patient's age, sex, and diet, the severity of any infection, time of administration and other clinical factors. The dosage may vary with the type of matrix used in the reconstitution and with inclusion of other proteins in the pharmaceutical composition. For example, the addition of other known growth factors, such as IGF I (insulin like growth factor I), to the final composition, may also effect the dosage. Progress can be monitored by periodic assessment of tissue/bone growth and/or repair, for example, X-rays, histomorphometric determinations and tetracycline labeling.

Polynucleotides of the present invention can also be used for gene therapy. Such polynucleotides can be introduced either *in vivo* or *ex vivo* into cells for expression in a mammalian subject. Polynucleotides of the invention may also be administered by other known methods for introduction of nucleic acid into a cell or organism (including, without limitation, in the form of viral vectors or naked DNA).

Cells may also be cultured *ex vivo* in the presence of proteins of the present invention in order to proliferate or to produce a desired effect on or activity in such cells. Treated cells can then be introduced *in vivo* for therapeutic purposes.

Patent and literature references cited herein are incorporated by reference as if fully set forth.

Table 3

Sel.	Species	Tissue	Cell Type
AA	Human	Kidney	19-23wks., M/F pool of 5
AB	Human	Fetal Lung	Fetal Lung
AC	Human	Placenta	26yrs., 1 specimen
AD	Murine	Embryo	Fetal ES cells
AE	Murine	Spleen	Adult spleen
AF	Murine	Fetal Brain	Fetal Brain
AG	Murine	Fetal Brain	Fetal Brain
AH	Murine	Fetal Thymus	Fetal Thymus
AI	Human	Blood	Adult PBMC/TH1or2
AJ	Human	Testes	10-61yrs., pool of 11
AK	Human	Kidney	19-23wks., M/F pool of 5
AL	Human	Neural	Adult Glioblastoma line TG-1
AM	Human	Kidney	19-23wks., M/F pool of 5
AN	Murine	Bone Marrow	Adult Stromal cell line FCM-4
AO	Murine	Thymus	Adult Subtr. Adult Thymus
AP	Human	Placenta	26yrs., 1 specimen
AQ	Human	Ovary	PA-1 Teratocarcinoma
AR	Human	Retina	16-75yrs., pool of 76
AS	Human	Brain	19-23wks., M/F pool of 5
AT	Human	Blood	Adult lymphocytes+dend. cells
AU	Human	Testes	10-61yrs., pool of 11
AV	Murine	Spleen	Adult spleen
AW	Human	Ovary	PA-1 Teratocarcinoma
AX	Human	Testes	10-61yrs., pool of 11
AY	Human	Retina	16-75yrs., pool of 76
AZ	Human	Colon	Caco-2 Adenocarcinoma
B	Human	Blood	PeripheralBloodMononuclearCell
BA	Human	Placenta	26yrs., 1 specimen
BB	Human	Blood	Adult PBMC/TH1or2
BC	Murine	Embryo	Fetal ES cells
BD	Human	Kidney	19-23wks., M/F pool of 5
BE	Human	Blood	Adult PBMC/TH1or2
BF	Human	Brain	19-23wks., M/F pool of 5
BG	Human	Brain	N/A
BH	Human	Ovary	PA-1 Teratocarcinoma
BI	Human	Kidney	19-23wks., M/F pool of 5
BJ	Human	Ovary	PA-1 Teratocarcinoma
BK	Human	Retina	16-75yrs., pool of 76
BL	Human	Testes	10-61yrs., pool of 11
BM	Human	Muscle	N/A
BN	Human	Placenta	26yrs., 1 specimen
BO	Human	Retina	16-75yrs., pool of 76
BP	Human	Kidney	19-23wks., M/F pool of 5
BQ	Human	Colon	Caco-2 Adenocarcinoma Caco2

BR	Human	Kidney	19-23wks., M/F pool of 5
BS	Human	Pituitary	Adult Pituitary
BT	Human	Blood	Adult PBMC
BU	Human	Placenta	26yrs., 1 specimen
BV	Human	Brain	N/A
BW	Human	Blood	Adult PBMC
BX	Human	Ovary	PA-1 Teratocarcinoma
BY	Human	Blood	Adult PBMC/TH1or2
BZ	Human	Kidney	19-23wks., M/F pool of 5
C	Human	Blood	PeripheralBloodMononuclearCell
CA	Murine	Embryo	Fetal ES cell embryoid bodies
CB	Human	Brain	19-23wks., M/F pool of 5
CC	Human	Brain	N/A
CD	Human	Brain	19-23wks., M/F pool of 5
CE	Human	Blood	Adult lymphocytes+dend. cells
CF	Human	Placenta	26yrs., 1 specimen
CG	Human	Testes	10-61yrs., pool of 11
CH	Human	Kidney	19-23wks., M/F pool of 5
CI	Human	Brain	N/A
CJ	Human	Brain	19-23wks., M/F pool of 5
CK	Human	Testes	10-61yrs., pool of 11
CL	Human	Retina	16-75yrs., pool of 76
CM	Human	Adult Lung	Adult Lung
CN	Human	Brain	19-23wks., M/F pool of 5
CO	Human	Brain	N/A
CP	Human	SalivaryGland	N/A
CQ	Human	Heart	13-73yrs., pool of 3
CR	Human	Testes	10-61yrs., pool of 11
CS	Human	Brain	19-23wks., M/F pool of 5
CT	Human	Brain	N/A
CU	Human	Pineal Gland	N/A
CV	Human	Mammary	Adult Human Mammary
CW	Human	Brain	19-23wks., M/F pool of 5
CY	Human	Pineal Gland	N/A
CZ	Human	Testes	10-61yrs., pool of 11
D	Human	Blood	PeripheralBloodMononuclearCell
DA	Human	Placenta	26yrs., 1 specimen
DB	Human	Prostate	Adult Prostate
DC	Human	Pineal Gland	Adult Pineal Gland
DD	Human	Testes	10-61yrs., pool of 11
DE	Human	Testes	Adult NCCIT TeratoCA
DF	Human	Brain	N/A
DG	Human	Placenta	26yrs., 1 specimen
DH	Human	Brain	19-23wks., M/F pool of 5
DI	Human	Testes	10-61yrs., pool of 11
DJ	Human	Placenta	26yrs., 1 specimen
DK	Human	Fetal Kidney2	Fetal Kidney

DL	Human	Brain	N/A
DM	Human	Brain	N/A
DN	Human	Brain	19-23wks., M/F pool of 5
DO	Human	Testes	10-61yrs., pool of 11
DP	Murine	Embryo	Fetal ES cell embryoid bodies
DQ	Human	Placenta	26yrs., 1 specimen
DR	Human	SalivaryGland	N/A
DT	Human	Brain	N/A
DU	Human	Brain	19-23wks., M/F pool of 5
DV	Human	Pineal Gland	Adult Pineal Gland
DW	Human	Brain	N/A
DX	Human	Testes	10-61yrs., pool of 11
DY	Human	Brain	N/A
DZ	Human	Testes	Adult NCCIT TeratoCA
E	Human	Blood	PeripheralBloodMononuclearCell
EA	Human	Brain	19-23wks., M/F pool of 5
EB	Human	Melanoma	Adult Melanoma
EC	Human	Brain	N/A
ED	Human	Placenta	26yrs., 1 specimen
EE	Human	Testes	10-61yrs., pool of 11
EF	Human	Liver	Adult Liver
EG	Human	Pancreas	Adult HPC-3 Ductal AdenoCA
EH	Human	Blood	PeripheralBloodMononuclearCell
EI	Human	Brain	19-23wks., M/F pool of 5
EJ	Human	Placenta	26yrs., 1 specimen
EK	Human	Brain	19-23wks., M/F pool of 5
EL	Human	Testes	10-61yrs., pool of 11
EM	Human	Fetal Kidney2	Fetal Kidney
EN	Human	Brain	19-23wks., M/F pool of 5
EO	Human	Adrenal Gland	Adult Adrenal Gland
EP	Human	Placenta	26yrs., 1 specimen
EQ	Human	Testes	10-61yrs., pool of 11
ER	Human	Brain	19-23wks., M/F pool of 5
ES	Human	Placenta	26yrs., 1 specimen
ET	Human	Testes	10-61yrs., pool of 11
EU	Human	Kidney	Adult Kidney
EV	Human	Stomach	Adult Stomach
EW	Human	Placenta	26yrs., 1 specimen
EX	Human	Testes	10-61yrs., pool of 11
EY	Human	Brain	19-23wks., M/F pool of 5
EZ	Human	Fetal Kidney2	Fetal Kidney
FA	Human	Brain	19-23wks., M/F pool of 5
FB	Human	Placenta	26yrs., 1 specimen
FC	Human	Testes	10-61yrs., pool of 11
FD	Human	SalivaryGland	N/A
FE	Human	Brain	N/A
FF	Human	Testes	Adult NCCIT TeratoCA

FG	Human	Brain	N/A
FH	Human	Brain	19-23wks., M/F pool of 5
FI	Human	Small Intest	Adult Small Intestine
FJ	Human	Lung CA	Adult Lung CA
FK	Human	Kidney	Adult Kidney
FM	Human	Brain	N/A
FN	Human	Brain	19-23wks., M/F pool of 5
FO	Human	Brain	N/A
FP	Human	Placenta	26yrs., 1 specimen
FQ	Human	Testes	10-61yrs., pool of 11
FR	Human	Placenta	26yrs., 1 specimen
FS	Human	Testes	10-61yrs., pool of 11
FT	Chicken	Fetal Lung	Fetal Lung
FU	Chicken	Limb Bud	Fetal St. 23 Limb Bud
FV	Human	Testes	Adult NCCIT TeratoCA
FW	Human	Testes	Adult NCCIT TeratoCA
FX	Human	Brain	19-23wks., M/F pool of 5
FY	Human	Placenta	26yrs., 1 specimen
FZ	Human	Placenta	26yrs., 1 specimen
G	Human	Blood	PeripheralBloodMononuclearCell
GA	Human	Testes	10-61yrs., pool of 11
GB	Human	Placenta	26yrs., 1 specimen
GC	Human	Testes	10-61yrs., pool of 11
GD	Human	Placenta	26yrs., 1 specimen
GE	Human	Brain	N/A
GF	Human	Brain	19-23wks., M/F pool of 5
GG	Human	Fetal Kidney2	Fetal Kidney
GH	Human	Placenta	26yrs., 1 specimen
GI	Human	Retinoblastoma	Adult Retinoblastoma Y79
GJ	Murine	Spleen	Adult Spleen
GK	Human	Fetal Kidney2	Fetal Kidney
GL	Murine	Lymph Node	Adult Lymph Node
GM	Human	Uterus	N/A
GN	Human	Blood	PeripheralBloodMononuclearCell
GO	Human	Adrenal Gland	Adult Adrenal Gland
GP	Human	Ovary	PA-1 Teratocarcinoma
GQ	Human	Pineal Gland	N/A
GR	Human	Pancreas	Adult HPC-3 Ductal AdenoCA
GS	Human	Retina	16-75yrs., pool of 76
GT	Human	Brain	N/A
GU	Human	Fetal Kidney2	Fetal Kidney
GV	Rat	Retina	Newborn Retina
GW	Chicken	Limb Bud	Fetal St.26 Limb Bud
GX	Human	Brain	N/A
GY	Human	Testes	10-61yrs., pool of 11
GZ	Human	Brain	19-23wks., M/F pool of 5
H	Human	Blood	PeripheralBloodMononuclearCell

HA	Human	Testes	Adult NCCIT TeratoCA
HB	Human	Fetal Kidney2	Fetal Kidney
HC	Human	Brain	19-23wks., M/F pool of 5
HD	Human	Brain	N/A
HE	Human	Testes	10-61yrs., pool of 11
HF	Human	Brain	19-23wks., M/F pool of 5
HG	Human	Fetal Kidney2	Fetal Kidney
HH	Human	Brain	N/A
HI	Human	Testes	10-61yrs., pool of 11
HJ	Human	Brain	N/A
HK	Human	Brain	19-23wks., M/F pool of 5
HL	Human	Fetal Kidney2	Fetal Kidney
HM	Human	Testes	Adult NCCIT TeratoCA
HN	Human	Fetal Kidney2	Fetal Kidney
HO	Human	Brain	N/A
HP	Human	Brain	19-23wks., M/F pool of 5
HQ	Human	Testes	10-61yrs., pool of 11
HR	Human	Brain	N/A
HS	Human	Brain	N/A
HT	Human	Brain	19-23wks., M/F pool of 5
HU	Human	Fetal Kidney2	Fetal Kidney
HV	Human	Testes	10-61yrs., pool of 11
HW	Human	Brain	N/A
HX	Human	Brain Hippoca	Adult Brain Hippocampus
HY	Human	Trachea	Adult Trachea
HZ	Human	Brain Thalamus	Adult Brain Thalamus
I	Human	Blood	PeripheralBloodMononuclearCell
IA	Human	Thyroid	Adult Thyroid
IB	Human	Embryonal CA	Fetal NT2-D1
IC	Human	WER1-Rb1 line	Adult Retinoblastoma
ID	Human	Muscle	N/A
IE	Human	Brain	19-23wks., M/F pool of 5
IF	Human	Uterus	N/A
IG	Human	Testes	10-61yrs., pool of 11
IH	Human	Muscle	N/A
II	Human	Brain	N/A
IJ	Human	Blood	PeripheralBloodMononuclearCell
IK	Human	Retinoblastoma	Adult Retinoblastoma Y79
IL	Human	Retina	16-75yrs., pool of 76
IM	Human	Various	Various
IN	Human	Prostate	Adult Prostate
IO	Human	Brain	19-23wks., M/F pool of 5
IP	Human	Fetal Kidney2	Fetal Kidney
IQ	Human	Prostate	Adult Prostate
IR	Human	Brain Hippoca	Adult Brain Hippocampus
IS	Human	Trachea	Adult Trachea
IT	Human	Brain Thalamu	Adult Brain Thalamus

SEQUENCE LISTING

(1) GENERAL INFORMATION:

(i) APPLICANT: Jacobs, Kenneth
McCoy, John
LaVallie, Edward
Racie, Lisa
Merberg, David
Treacy, Maurice
Spaulding, Vikki
Agostino, Michael

(ii) TITLE OF INVENTION: SECRETED, EXPRESSED SEQUENCE TAGS

(iii) NUMBER OF SEQUENCES: 1500

(iv) CORRESPONDENCE ADDRESS
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(D) STATE: Massachusetts
(E) COUNTRY: U.S.A
(F) ZIP: 02140

(v) COMPUTER READABLE FORM:
(A) MEDIUM TYPE: Floppy Disk
(B) COMPUTER: IBM PC Compatible
(C) OPERATING SYSTEM: PC-DOS/MS-DOS
(D) SOFTWARE: PatentIn Release #1.0, Version #1.30

(vi) CURRENT APPLICATION DATA:
(A) APPLICATION NUMBER:
(B) FILING DATE:
(C) CLASSIFICATION:

(vii) ATTORNEY/AGENT INFORMATION:
(A) NAME: Brown, Scott A.
(B) REGISTRATION NUMBER: 32,724

(ix) TELECOMMUNICATION INFORMATION:
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(2) INFORMATION FOR SEQ ID NO:1:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 335 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:1:

GTCGACCCCA TCCCATCCAA TAGTCCCCAT CTCTTCTCAG CTCTCTCTGT AGTTTCTCTT 60
CCTCCGCCTG CCTTTTAAGT TAGTGTTTCC CAGGACAGAG GTGACTCAGT TGTATCCAGA 120
CCGCTCTGTG ACTGAACACC CACTTTCTTT TCCTTTTCCA ATAAATATAT GTAACATACA 180
TGTCAACTAG GAACAAAACA GTATCTCAGG AATCCACCAT CCAGTTAAAA ATGGACCCTT 240

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 98/06954

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C12N15/12 C12N5/10 C07K14/47 C12Q1/68 A61K38/17

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C12N C07K C12Q A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 97 07198 A (GENETICS INSTITUT) 27 February 1997 see the whole document ---	1-8
A	WO 97 04097 A (GENETICS INST) 6 February 1997 ---	1-8
A	ADAMS M D ET AL: "3,400 NEW EXPRESSED SEQUENCE TAGS IDENTIFY DIVERSITY OF TRANSCRIPTS IN HUMAN BRAIN" NATURE GENETICS, vol. 4, no. 3, July 1993, pages 256-267, XP000611495 see the whole document --- -/--	1-8

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
3 July 1998	30.09.98

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	HORNIG H.

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 98/06954

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5 536 637 A (JACOBS KENNETH) 16 July 1996 cited in the application see the whole document	1-8
A	JACOBS K ET AL: "A NOVEL METHOD FOR ISOLATING EUKARYOTIC CDNA CLONES ENCODING SECRETED PROTEINS" JOURNAL OF CELLULAR BIOCHEMISTRY - SUPPLEMENT, vol. 21A, 10 March 1995, page 19 XP002027246 see abstract	1-8
A	WO 90 14432 A (GENETICS INST) 29 November 1990 see the whole document	1-8
A	WO 96 17925 A (IMMUNEX CORP) 13 June 1996 see the whole document	1-8

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Int tional application No.
PCT/US 98/06954

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see further information sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

see further information sheet, subject 1.

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

Invention 1. Claims: (1-8) partially

An isolated polynucleotide comprising a nucleotide sequence selected from SEQ ID no.1, consisting of a nucleotide sequence selected from SEQ ID no.1, consisting essentially of a nucleotide sequence selected from SEQ ID no.1; an isolated polynucleotide comprising a nucleotide sequence which hybridizes to a sequence consisting of SEQ ID no.1; an isolated protein encoded by said isolated polynucleotides;

Inventions 2 to 1500. Claims: (1-8) partially

Idem as subject 1 but limited to SEQ ID nos.2 to 1500 respectively clone ID nos. B11 to BV29. (Invention 2 is limited to SEQ ID. no. 2; Invention 3 is limited to SEQ ID no. 3;.....Invention 1500 is limited to SEQ ID no. 1500);

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/US 98/06954

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9707198 A	27-02-97	US 5707829 A	13-01-98
		AU 6712396 A	18-02-97
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		EP 0839196 A	06-05-98
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